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British Heart Journal

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Walmsley R. Anatomy of left ventricular outflow tract. *Br Heart J* 1979; **41**: 263–7.

(2) *Books and other monographs:*
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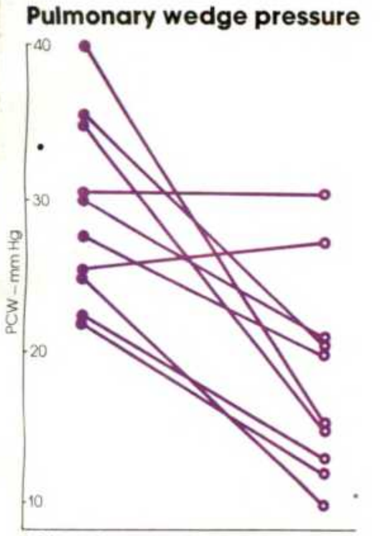
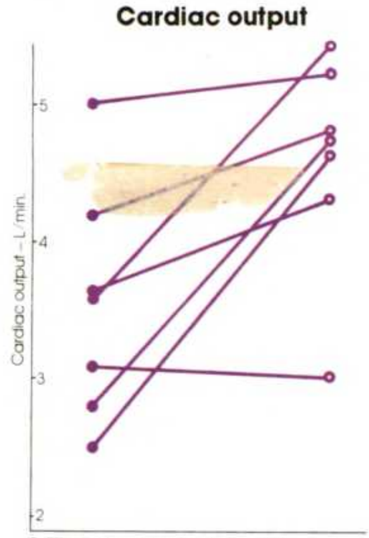
n moderate to severe heart failure unresponsive to digitalis and diuretics the goal of therapy is to reduce elevated pulmonar rterial and left ventricular end-diastolic pressures and increase cardiac output whilst minimizing any fall in arterial pressure.[1]

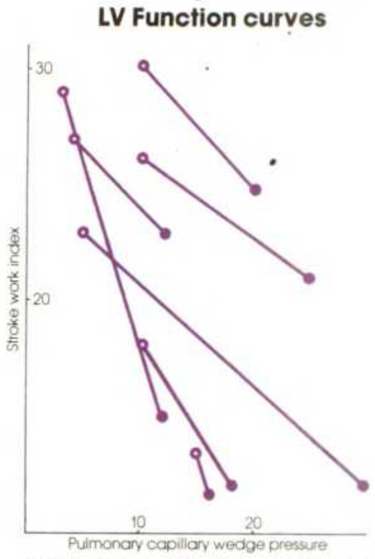


1. Effects of isosorbide dinitrate (Isoket) on pulmonary capillary wedge pressure.

PRIOR TO ISOKET ● ON "OPTIMAL" DOSE OF ISOKET ○



2. Effects of Isoket on cardiac output.



3. Effects of Isoket on left ventricular function curves.

soket* ampoules

osorbide dinitrate 1mg/ml)

proven effective in heart failure

et was administered i.v. in doses of 2-7 mg/hour 10 patients suffering from extreme pump failure fractory to conventional therapy. Seven patients d severe coronary disease with recurrent arctions; 5 receiving Isoket during an acute event d in 3 of them severe mitral regurgitation was cumented. Three other patients received Isoket t prior to surgery with heart failure consequent to a ptured ventricular septum, aortic insufficiency and severely leaking mitral prosthesis.

Marked haemodynamic improvement during oket manifested by decrease of pulmonary wedge essure (PWP) and systemic vascular resistance ith increase of cardiac output was obtained in 7 of e 10 patients studied.

Mean arterial pressure was "markedly and avourably affected in those patients who had igh initial pressures. The lower arterial ressures remained stable or even increased little in two patients." Heart rate and the nsmyocardial gradient were not deleteriously ected.

oket also produced a complete abolition of the al regurgitation as evidenced by the disappearance of the giant 'V' wave on the PWP tracings.

The authors concluded that Isoket appears to be highly effective and rather safe drug in properly onitored patients with pump failure."[2]

opy of this clinical paper, further information d a data sheet are available from:
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es, 130 High Street, Chesham, Bucks. HP5 1EF Tel. (0494) 772071

Prescribing Information

Presentation Ampoules containing 10 mg Isosorbide dinitrate in 10 ml of colourless sterile isotonic saline. **Uses** Isoket i indicated in the treatment of unresponsive left ventricular failure secondary to acute myocardial infarction, unresponsiv left ventricular failure of various aetiology and severe or unstable angina pectoris. Isosorbide dinitrate is a vasodilato reducing the afterload and especially the preload of the heart. It influences the oxygen supply to ischaemic myocardiun by causing the redistribution of blood flow along collateral channels and from epicardial to endocardial regions. It als reduces oxygen demand by increasing venous capacitance, causing pooling of blood in peripheral veins thereb reducing ventricular volume and heart wall distension. **Dosage and Administration** *Dosage* The dose employed mus be adjusted according to the patient's response. In general, a dose of between 2 and 7 mg per hour is suitable, althoug doses as high as 10 mg per hour may be necessary. *Children* The safety and efficacy of Isoket has not yet been establishe in children. *Administration* Isoket is a concentrated solution and should never be injected directly. It should always b administered as an intravenous admixture with a suitable vehicle such as Sodium Chloride Injection B.P. or Dextros Injection B.P. Prepared Isoket admixtures are always given by intravenous infusion or with the aid of an infusion pump During administration, there should be close monitoring of the patient's blood pressure and pulse. Admixtures are pre pared by exchanging the required volume of Isoket with an equal volume of the infusion vehicle. **For example, if a dos of 6 mg per hour is required, 50 ml of Isoket (equivalent to 5 x 10 ml ampoules) should be added to 450 ml o the infusion vehicle to give a final volume of 500 ml. This admixture now contains 1 mg in 10 ml and the require dosage can be obtained by giving 60 ml per hour which is equivalent to a drip rate of 60 paediatric microdrops per minute or 20 standard drops per minute. This drip rate provides enough solution for an infusion tim of 8 hours and 20 minutes. Contra-indications and Warnings, etc.** *Contra-indications* Isoket should not be used i the treatment of cardiogenic shock unless some means of maintaining an adequate diastolic aortic pressure ar undertaken. Isoket is contra-indicated in circulatory collapse and severe hypotension. *Precautions* Close attention t pulse and blood pressure is necessary during the administration of Isoket infusions. *Adverse Effects* Whilst sharp falls i systemic arterial pressure can give rise to symptoms of cerebral flo deficiency and decreased coronary perfusion, clinical experience wi Isoket has shown that this is not normally a problem. This is consistent wi the known vasodilatory effects of Isosorbide dinitrate which occ predominantly on the venous rather than the arterial side of the circulatio In common with other nitrates, headache and nausea may occur durin administration. **Pharmaceutical Precautions** *Compatibility* **Isoke contains Isosorbide dinitrate in isotonic saline and is compatibl with commonly employed infusion solutions. No incompatibilitie have so far been demonstrated. Isoket is compatible with glas infusion bottles and infusion packs made of polyethylene, e.g Polyfusor (Boots) or Bottle-Paks and Flat-Paks distributed b Dylade, Cheshire. Isoket may be infused slowly using a syring pump with a glass or rigid plastic syringe (Gillette Sabre syring or Brunswick Disposable Plastipak syringes).** Isoket is incompatibl with infusion bags and administration sets made from PVC and a loss o activity of up to 40% is possible on prolonged contact, e.g. 8 hours. Loss after 1 hour is approximately 30%. The use of PVC containers should therefore be avoided, e.g Viaflex (Travenol) or Steriflex (Boots). **Legal Category** POM. **Package Quantities** Each pack contains ten ampoules of Isoket. **Further Information** Nil. **Product Licence** PL 4438/0001. **Basic NHS Cost** £49.50 per pack of 10 ampoules.

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1. W.W. Parmley and K. Chatterjee: "In coronary care: Congestive heart failure." American Heart Association (1977).

2. Rabinowitz B et al., In Nitrates II, 2nd Int. Nitrate Symp., Eds. Rudolph & Schrey, Urban & Schwarzenberg (1980).

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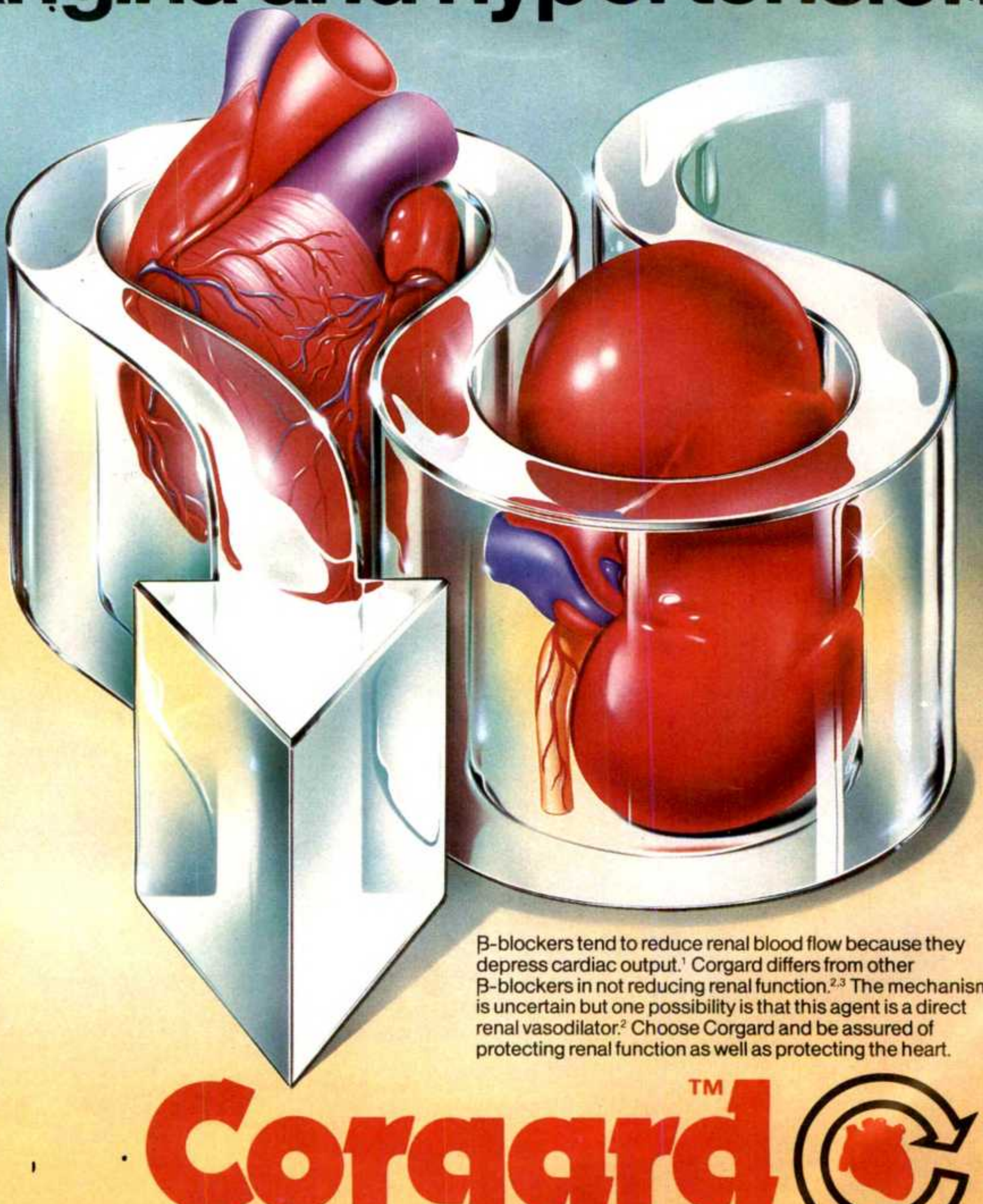

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References

1. Lancet 1980; 1: 693 2. Br J clin Pharm 1979; 7: (Suppl 2) 219S 3. In: Gross F, ed. International Experience with Nadolol – a long-acting β-blocking agent: symposium, Paris, December 5–7, 1980 London: R Soc Med No 37 1981 25–30

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References: 1. Aronow WS. Effect of Cigarette Smoking and of Carbon Monoxide on Coronary Heart Disease. Chest 1976; 70: 54-157. 2. Tibblin G, Wilhelmsen L, Werkö L. Risk Factors for Myocardial Infarction and Death Due to Ischemic Heart Disease and Other Causes. American Journal of Cardiology 1975; 35: 514-522. 3. Russell MAH, Wilson C, Taylor C, Baker CD. Brit med J 1979; 2: 231-235. 4. Raw M, Jarvis MJ, Feyerabend C, Russell MAH. Brit med J 1980; 281: 481-482.

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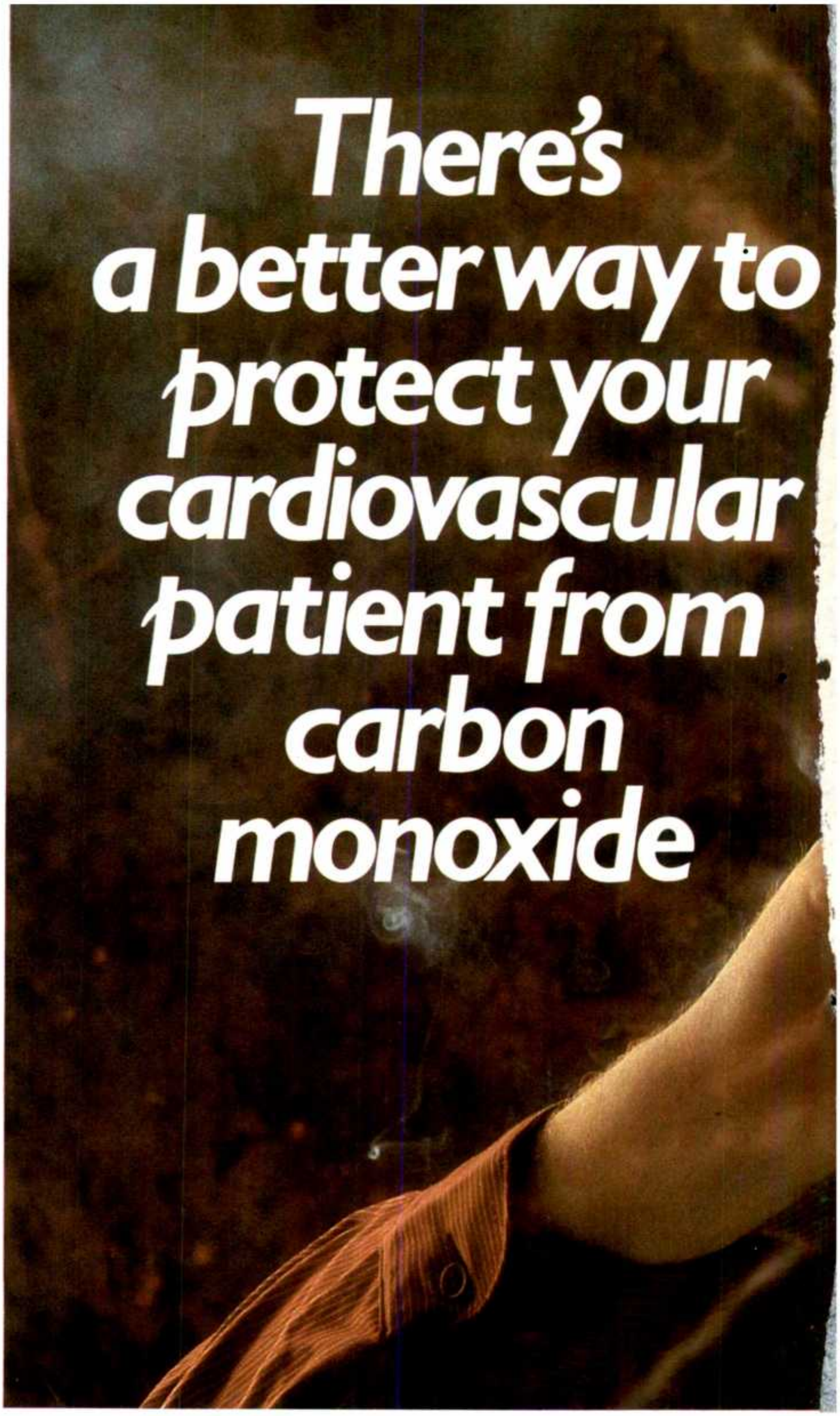

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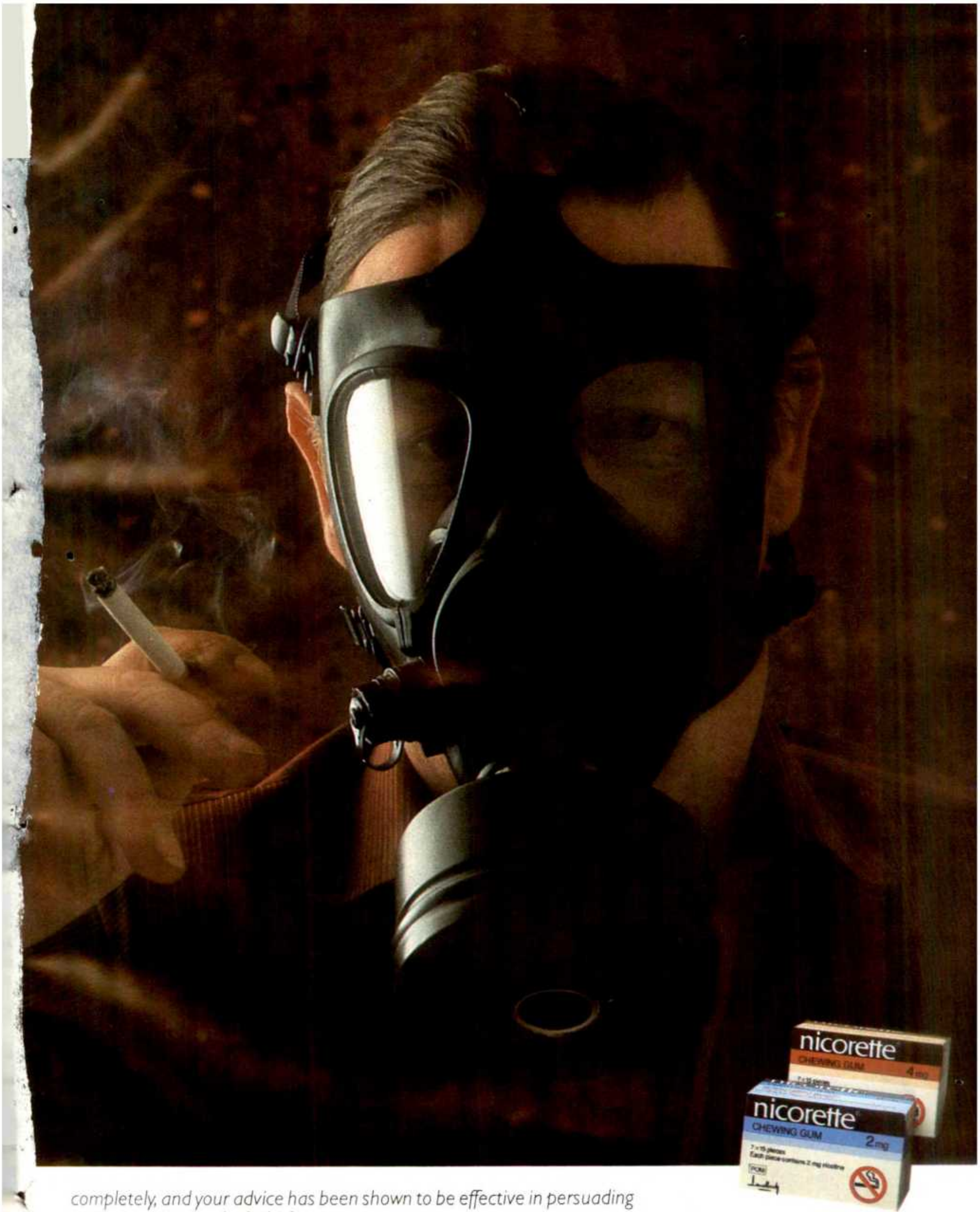

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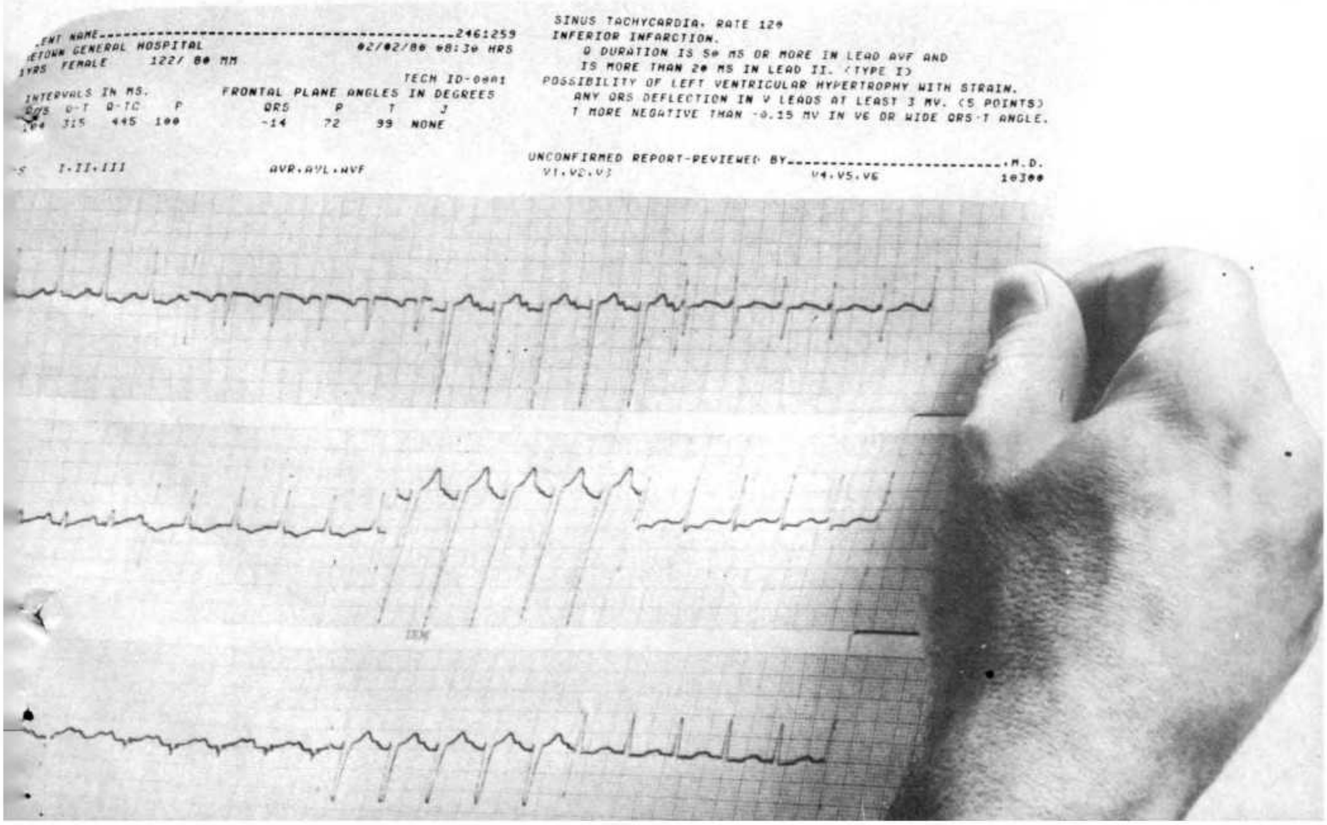

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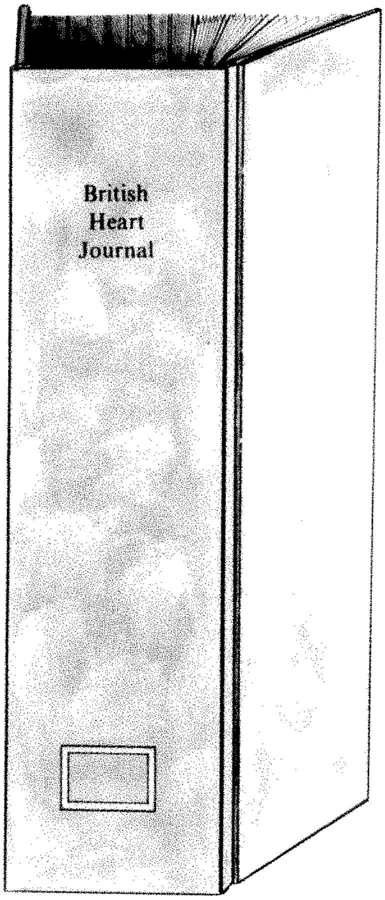

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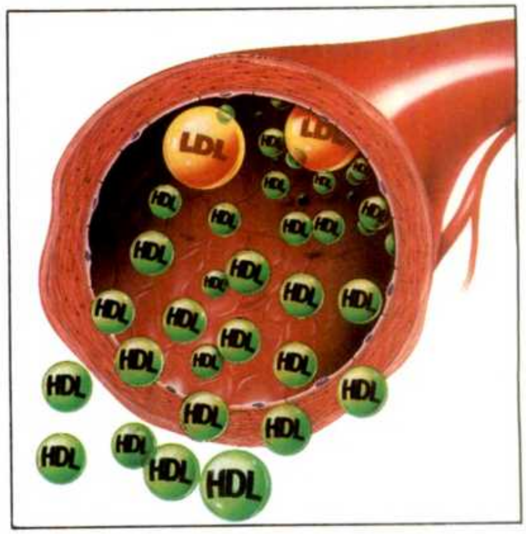

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1. *JAMA*, **62** (1977) 707
2. Manufacturers' Literature
3. Lipoproteins and Coronary Heart Disease, Witzstrock Publishing House, New York (1980) 185-188
4. *Ibid*: 192-195
5. *Munch. med. Wschr.* **122, 5** (1980) 165-168
6. Diet and Drugs in Atherosclerosis, eds. G. Noseda, B. Lewis, R. Paoletti, Raven Press, New York (1980) 137-142

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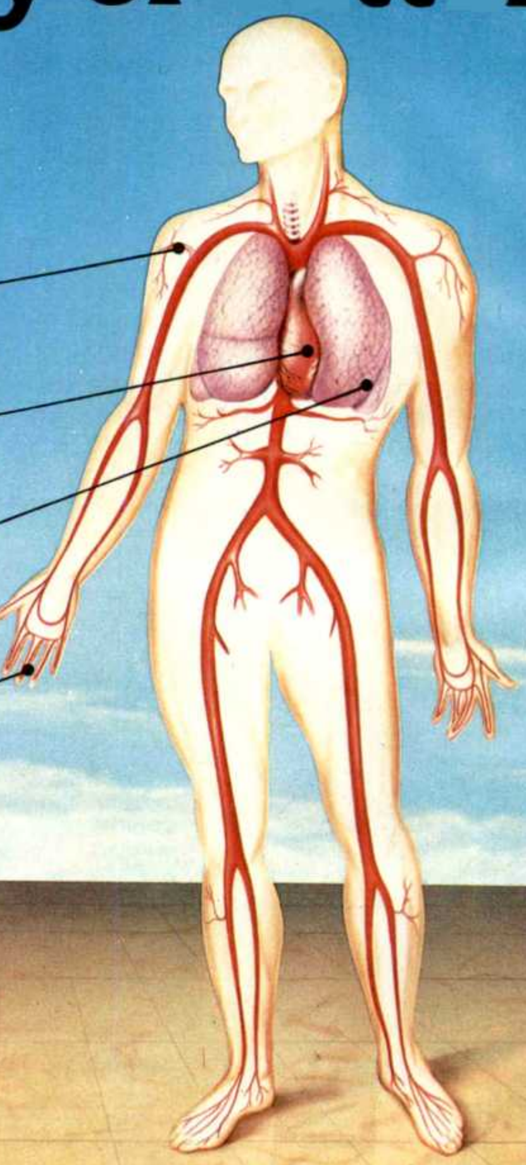
The anatomy of better B.P. control



New Baratol works in the arterioles[1,2]

As an alpha-blocker, Baratol lowers BP by reducing peripheral resistance —widely considered as the most logical way to treat hypertension.

And keeps the heart rate stable[1,2]

For the first time ever, Baratol combines alpha-blockade with a stabilising effect on the myocardium—the heart rate is not changed significantly and in particular there's no marked slowing of the heart.

Useful in asthmatics and bronchitics[3]

Unlike beta-blockers, Baratol can be used with confidence in 'wheezy chest' patients because bronchoconstriction does not occur.

Cold extremities are not a problem[3]

Troublesome side-effects often seen with beta-blockers e.g. cold hands and feet, are avoided with Baratol.

Alone or in combination[1,5]

Baratol is effective on its own or with a diuretic for the routine treatment of all grades of essential hypertension.

Simple dosage—25mg bd, add 25mg at 2 week intervals until control is achieved.

NEW

Baratol α

indoramin

the alpha-blocker that reduces peripheral resistance _and_ keeps the heart rate stable

cribing Information. For full information see product data sheet. **BARATOL Presentation**: Baratol tablets contain indoramin hydrochloride; the 25mg tablets are blue and the 50mg tablets are green. **Uses**: All grades of
itial hypertension. **Dosage and administration**: For full details see Data Sheet. Initial dose: 25mg b.d. for all patients. Dose titration: Dosage should be titrated at 2 week intervals to control B.P. to a maximum of 200mg daily
nti-hypertensive effect is enhanced by concomitant administration of a thiazide diuretic or a beta-adrenoceptor blocking drug. **Contra-indications, Warnings, etc.** *Contra-indications* – Patients with established heart failure
ients under treatment with MAOI.s. *Precautions* – Drowsiness is sometimes seen in the initial stages of treatment or when dosage is increased too rapidly. Patients should be warned not to drive or operate machinery until it
ablished that they do not become drowsy while taking BARATOL. Incipient cardiac failure should be controlled with diuretics and digitalis before treatment with BARATOL. Caution should be observed in
nts with hepatic or renal insufficiency or Parkinson's disease. Animal experiments indicate no teratogenic effects but BARATOL tablets should not be prescribed for pregnant women unless considered
itial by the physician. *Side-effects* – Sedation occurs in some patients but is rarely intolerable and is usually overcome by a modest reduction in dosage. Less commonly dry mouth, nasal congestion, weight
dizziness, failure of ejaculation and depression have also been noted. **Treatment of overdosage** – See product data sheet. **Legal category**: POM. **Package quantities**: Bottles of 100. **Basic NHS Price**: 25mg
£11.00. 50mg 100s £19.50. **Hospital Price**. As per local contract. **Product Licence number**: 25mg tablets PL0011/0071. PA 22/34/1. 50mg tablets PL 0011/0058. PA 22/34/2. **References** 1. Archibald, J.L.
) *Pharmacology of anti-hypertensive drugs*. Ed. Scriabine, A., Raven Press, N.Y. 161. 2. Coltart, J. (1981) *Brit. J. Clin. Pharmacol.*, **12**. 3. Zacharias, F.J. (1981) *Brit. J. Clin. Pharmacol.*, **12**. 4. Fitzgerald, M.V.J.
) *Brit. J. Clin. Pharmacol.*, **12**. 5. Johnson, E. S. (1981) *Brit. J. Clin. Pharmacol.*, **12**. Further information is available on request. **Wyeth Laboratories**, John Wyeth & Brother Ltd., Taplow, Maidenhead, Berks.
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Br Heart J 1982; 47: 1–10

Immunological probes in cardiovascular disease*

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SUMMARY The immune system has long been recognised as playing a central role in the organism's defence against infectious diseases and possibly the development of neoplasia. The active stimulation of the immune system by immunisation and the passive administration of antitoxins have a venerable history in medicine. Yet the concept that antibodies may be used to modify physiological or pharmacological effects or may act as diagnostic agents in the living organisms has only recently come to be recognised. Advances, both in an understanding of the structural chemistry of the antibody molecule and in the ability to culture antibody-producing cells, now permit the selection and production of homogeneous antibodies and their smaller fragments in quantity by means other than conventional immunisation. These innovations will allow the development of a new pharmacology based on the remarkable resolving power of the antibody combining site. Antibodies or their fragments are shown to inhibit the pressor action of renin, to neutralise the pharmacological actions of digitalis, to block the beta-adrenergic receptor, and to detect and image myocardial infarcts.

Antibodies represent a set of molecules that exhibit extraordinary specificity and selectivity. This has been appreciated since the work of Landsteiner,[1] who, in the early years of this century, was able to provide examples such as the ability of an antiserum to resolve the d and l stereoisomers of a simple aliphatic molecule, tartaric acid. More complex organic compounds that vary only by a single substituent group (such as the steroids, or digoxin and digitoxin, which differ in one hydroxyl group) may be readily separated.[2] The general structure of the antibody molecule is remarkably conserved, so that it is difficult for the chemist to tell the difference between two antibodies of varying specificity. There is a small region of the molecule, however, that is highly variable in its structure (the complementarity region) and makes up the surface that binds antigen. It is the amino acid sequence in this complementarity region that determines the nature of the antigen recognised. Recent work has uncovered the mechanisms responsible for variation in the amino acid sequence of the complementarity region.

The antibody molecule comprises four polypeptide chains, two identical light and heavy chains. The variable region of the light chain is the product of two genes: V, which occurs in several hundred copies, and J, of which four copies have been identified.[3–6] V and J of the light chain may occur in any combination. The heavy chain's variable region is the product of three genes: V, in several hundred copies, D, in 10 or more copies, and J, in four copies.[7 8] As in the light chain, any permutation and/or combination of these genes may occur. These mechanisms alone account for 107 different antibodies. In addition, somatic-point mutation has been shown to occur. Thus the number of possible antibodies must actually exceed 10^{10}.

Clinicians have not neglected the immune system, but its deliberate manipulation has been restricted to a limited number of areas. Of course, immunisation has long been a cornerstone of preventative medicine. The passive infusion of pneumococcal-specific antisera had a brief vogue in pre-antibiotic days, while tetanus and Rh antibodies are still of great value today. By providing a method for measuring substances in biological fluids that would not be possible by any other means, the immunoassay has produced a literal explosion in the use of antibodies as in vitro diagnostic agents. Yet, aside from these few uses, this remarkable group of compounds has been largely neglected in its potential utility as a source of pharmaceutical agents with both diagnostic and therapeutic applications.

There may be several explanations for this neglect.

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*Modified from the text of the International Lecture of the International Society and Federation of Cardiology delivered at the Royal College of Physicians, London on 4 December 1980.

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Before very recent times, antibodies were only available as complex mixtures of proteins, isolated in very limited quantities from animal sera. Standardisation of an antibody is not possible since each immunised animal provides an antiserum of different properties. There is even variation among specimens of sera of single animals at different times after immunisation. An additional problem is the potential immunogenicity of heterologous antibodies in the recipient. Each of these problems has been overcome by application of a new technology that has only been available in the past several years. Antibodies may now be produced by cell culture methods in infinite quantities with previously unimagined homogeneity and reproducibility.[9] Antibody fragments may be created that reside within the body for shorter periods of time and are less likely to provoke an immune response.[10] We are on the threshold of producing human antibodies by the same cell-culture approach.[11 12]

I shall review the potential application of antibodies to human pharmacology in four different areas: inhibition of the action of a hormone that is secreted in excess, blockade of a physiological receptor, detection of a newly exposed antigen in the living organism, and neutralisation of the toxic effect of a drug.

Blockade of physiological action of renin by specific antibody

Though renin has been known to play a role in circulatory control since the classic work of Goldblatt *et al.* in the 1930's,[13] its precise importance in a number of specific circumstances has been in doubt. Much has been learned from the application of inhibitors directed at several of the steps in the sequence leading to the production and action of the final product of renin, angiotensin II.[14] Most of these compounds lack specificity.[14] The competitive inhibitors, such as saralysin, of angiotensin II's action on receptors are partial agonists. The angiotensin-converting enzyme is identical to the enzyme that inactivates bradykinin,[15] and thus its inhibitors also affect the kinin system. In addition, compounds such as captopril have been shown to stimulate prostaglandin synthesis.[16] Since both the kinin and the prostaglandin systems have an effect on vasoregulation, it is difficult to define the specific part that renin plays in interpreting experiments in which these inhibitors are used. A specific antibody for renin should be a highly selective antagonist. Renin antibodies have been used as physiological reagents for many years,[17 18] yet their specificity has been in doubt since we now know that the preparations then used as immunogens contained less than 1% of the enzyme.

Dzau *et al.*[19] in our laboratory purified canine renin some 600 000-fold in an eight-step process that yielded a product homogeneous by several criteria. Antibodies specific for purified canine renin produced in a goat inhibited the pressor action of the enzyme but did not modify the capacity of either angiotensin I or II to raise blood pressure.[20] This antibody preparation did not have any effect on the haemodynamics of the unanaesthetised, sodium-replete dog, while a significant hypotensive effect was noted in the sodium-depleted dog when the immunoglobulin G fraction from an antiserum was injected intravenously. Parallel to the fall in blood pressure, a decrease in both plasma renin activity and angiotensin II concentrations was observed, indicating that the antibody was exerting its effect by inhibiting the enzymatic action of renin on its substrate.

Intact antibody has a number of troublesome properties when used as a drug. When the source is a heterologous species, it is an immunogen. After the first use, an immune response develops that may result in anaphylaxis, serum sickness, or at best accelerated elimination. Pharmacological effects may be very persistent, because antibody is eliminated either by metabolism or by the immune system if sensitisation has occurred. The half-life for endogenous immunoglobulins may be measured in days or weeks depending on the species studied, the immunoglobulin's isotype, and whether or not the recipient has been immunised. When there is concern about renal function, the presence of immune complexes is likely to cloud interpretation. In haemodynamic studies, vasoactive peptides released by activation of complement may have independent effects, particularly on haemodynamics.

Some of these problems may be minimised by producing antibody fragments. Immunoglobulin molecules that bind two moles of antigen per mole may be cleaved to smaller molecules by the enzyme papain.[21] This results in two Fab that each bind one mole of antigen and one Fc that contains the complement binding site. Fab and Fc may be separated readily. Fab has a number of desirable properties when compared with the intact molecule, IgG: equilibrium distribution in extracellular fluid is achieved more rapidly; the volume of distribution is greater; and the fragment is eliminated with a far shorter half-life.[10] In addition, when injected intravenously, Fab is less immunogenic than IgG.[10] The immune complexes that may be formed are smaller than those that cause nephrotoxicity (comprising a single antigen molecule with several Fab attached), and complement cannot be fixed because the relevant binding sites on the Fc have been lost.

Renin-specific Fab has been used to block the action of renin in both sodium-depleted unanaesthetised dogs as well as in uninephrectomised dogs made hypertensive by constriction of the renal artery. In both models, intravenous injection of Fab results in a hypotensive response (Fig. 1). When compared with intact antibody, the initiation of hypotension by Fab is more rapid, and the duration very much shorter. Repetitive experiments have been possible in the same animal without the problem of anaphylaxis that had been experienced previously when intact antibody had been used.

An antiserum is a mixture of several hundreds of antibodies, all capable of binding to the immunising antigen. These antibodies vary considerably both with respect to affinity for the antigen and specificity of recognition. The mixture of antibodies contained within an antiserum is different among even inbred (genetically identical) individual animals, as it is in the sera of a single animal collected at varying times after immunisation. Supplies of antisera are necessarily limited. Köhler and Milstein[9] showed that antibodies might be produced in a very different manner. The technique of somatic-cell fusion allows for the production of hybrid cells. If the precursors of the hybrid are normal lymphocytes and cells from a malignant plasmacytoma, one can incorporate both properties of antibody production and growth in vitro into the product (colloquially named "hybridoma"). Cells that grow in culture may be cloned, so that all the progeny are daughters of a single precursor cell. A homogeneous culture of this type produces a single antibody that is uniform in structure and antigen binding properties. Since the cultures may be stored indefinitely at low temperatures, the same antibody may always be recovered. The amount of renin-specific antibody available from conventional sera was severely limited; we set out, therefore, to make monoclonal renin-specific antibodies by the somatic-cell fusion method,[22] making production in industrial quantities possible. Fig. 2 shows the binding to immobilised renin by a monoclonal antibody. We look forward to using monoclonal antibodies as more specific reagents that are available in indefinite quantities in the dissection of the physiology and chemistry of the renin-angiotensin system.

Blockade of beta-adrenergic receptor

The hormone receptors of the cell's plasma cell membrane are present in a very small number of copies (10 000 to 50 000 per cell), which makes their isolation exceedingly difficult. Antibodies to partially purified receptor preparations have been elicited,[23] but their utility is limited because they probably contain antibodies to other membrane constituents. The hormones or drugs that bind to receptors, however, are usually readily available in quantity. Frequently they are either peptides of modest size or synthetic organic compounds. For some receptors, several antagonists have been synthesised.

Could an antibody for the receptor be obtained by using the ligand (agonist or antagonist) as a template? The vast diversity of antibody combining sites, as already suggested, provides the potential for creating a complementary fit to almost any shape. If a figurative plaster mould could be cast upon the surface of the ligand that bound to the receptor, then a second

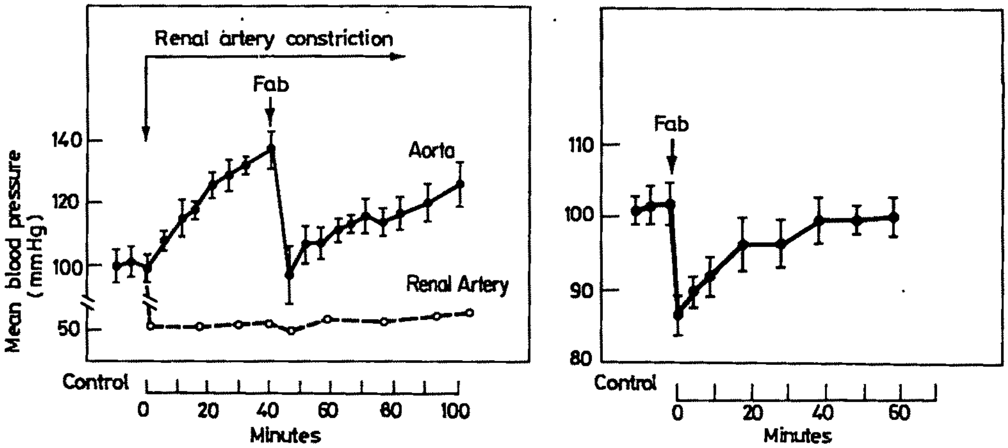

Fig. 1 *Renin-specific Fab was administered intravenously to either uninephrectomised dogs that were hypertensive as a result of constriction of the renal artery (left) or sodium-depleted dogs (right). In both experiments the rate of fall in blood pressure is more rapid and the duration shorter than observed with intact antibody.*

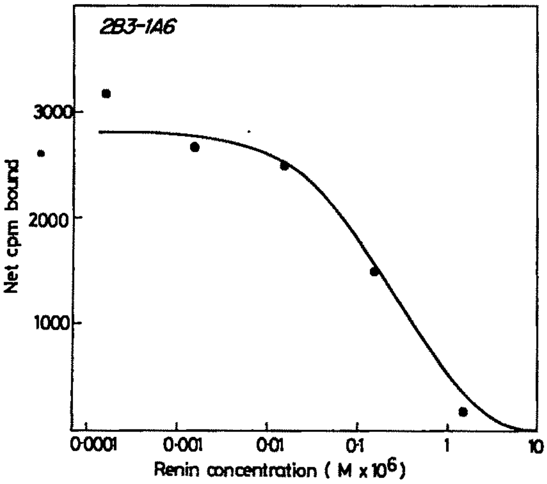

Fig. 2 *Competitive radioimmunometric assay of antibody 2B3-1A6. Renin is bound to the plastic microtitre plate and then incubated with the monoclonal antibody solution. The ordinate represents binding of* ^{125}*I goat anti-mouse Fab to IgM monoclonal antibody 2B3-1A6. Varying concentrations of soluble renin (abscissa) are added to the antibody solution before its application to immobilised renin. (Reprinted with permission of the American Heart Association, Inc.* Hypertension, *in press, 1981.)*

mould made from the first one should have a perfect fit to the receptor. The well-known immunological principle of raising antibodies specific for another antibody's combining site (anti-idiotypic antibodies) may be used as the vehicle for moulding the desired shape. Certain refinements are needed to achieve the desired end. Only some of the atoms of either a hormone or an antagonist bond to the receptor. The rest of the structure is needed to stabilise the active site or possibly to protect it from degradation. To achieve the desired result, the first antibody must bind the ligand generally in the same way as the receptor does, and thus the same atoms and interatomic interactions must be used. There are two ways of achieving this end short of depending on fortuitous probability.

When conventional immunisation is employed, many antibodies to the immunogen are formed, each binding to it in a somewhat different manner. Some are relevant to the part of the ligand that binds to the receptor, while others are not. The antibodies of this polyclonal response may be fractionated by the use of ligands of different structure. By virtue of being receptor ligands, they are all capable of binding to the receptor and must have some common structures. If appropriately selected, structures irrelevant to receptor binding are not shared. Those components of the polyclonal antibody mixture that bind to a number of dissimilar ligands are likely to be similar to the receptor. The most practical way of achieving fractionation with polyclonal antibodies is sequential affinity chromatography, a technique that employs a variety of ligands to capture the antibodies that bind to them. This general approach has now been applied successfully to the insulin receptor[24] and in our own laboratory to the beta-adrenergic receptor.[25-27]

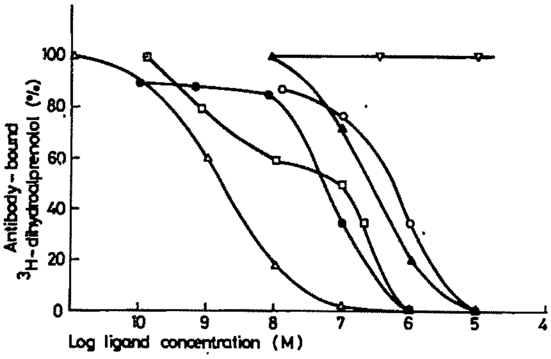

Fig. 3 *Competitive inhibition of (-)-[*^{3}*H]dihydroalprenolol binding to unfractionated anti-alprenolol antiserum. Rabbit immune serum (100 µl) was diluted 1:10 in buffer and incubated for one hour at 25° C with (-)-[*^{3}*H]dihydroalprenolol and increasing concentrations of (±)-propranolol (△), (±)-alprenolol (□), (±)-hydroxybenzylpindolol (●), (±)-norepinephrine (○), (±)-isoprenaline (▲), or catechol (▽). Each determination was performed in triplicate and corrected for the nonspecific (-)-[*^{3}*H]dihydroalprenolol binding to rabbit preimmune serum. The results are expressed as a percentage of the total antibody-binding capacity for the tritiated antigen. (Reprinted with permission of the American Heart Association, Inc.* Circ Res *1980; 46: 808–13.)*

There is a wide variety of structurally different beta-antagonists available. All, however, share a common structure, a propanolamine side chain. Rabbits were immunised with the beta-antagonist alprenolol conjugated to a protein. The resulting antiserum was passed over an affinity column to which another beta-antagonist had been linked and all that was not bound was discarded. The column was then washed with 1-propranolol and the eluted antibody retained. Fig. 3 shows the specificity profile of this antibody fraction. Several beta-adrenergic antagonists as well as agonists are bound with considerable affinity, in some cases similar to that of the receptor. This fraction also resolved 1 and d stereoisomers of isoprenaline (not shown). Thus the antibody fraction could be viewed as a qualitative, but not a strictly precise quantitative, model for the beta-adrenergic receptor.

Table *Inhibition of [^3H]alprenolol binding to antibodies and receptors by anti-idiotypic antibody**

	Maximal binding with preimmune (DPM)	*In presence of anti-idiotype (DPM)*	*Inhibition (%)*
Original idiotype (alprenolol)	10853 ± 250	488 ± 250	96%
Turkey erythrocyte	19643 ± 540	6195 ± 525	68%
Canine lung	6385 ± 283	4315 ± 190	34%

*Specific binding at 4-6 nM [^3H]alprenolol.

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Antibodies specific for the antigen binding regions (complementarity regions) of the first antibody set were then raised by immunisation of rabbits that were genetically identical with respect to immunoglobulin constant region structures. Because of tolerance to self-determinants, the immunised animals made antibodies only to the variable regions, the unique structures on the immunogen. The antigenic determinant of an immunoglobulin that is characteristic of a single antibody species is called an idiotype, and antibodies directed towards that determinant are named anti-idiotypes. The Table shows the inhibition of binding of a labelled beta-adrenergic antagonist, [^{3}H]-alprenolol, to several kinds of binding sites by the anti-idiotypic antibody. Binding of the ligand, alprenolol, to the idiotype (the first generation antibody that had been raised in response to alprenolol) is largely inhibited by anti-idiotype (second-generation antibody). Of greater interest is the inhibition of the specific binding of alprenolol to plasma membrane preparation in two different animal species. Quantitative analysis of binding shows it to be of a competitive nature, analogous to that shown by conventional beta-antagonists.

The anti-idiotype is also an inhibitor of adenylate cyclase activation by beta-adrenergic agonists. Increasing concentrations of isoprenaline progressively inhibit adenylate cyclase production in turkey erythrocyte membranes at 5×10^{-7}M isoprenaline concentration. At a higher concentration of isoprenaline (10^{-4}M), less inhibition is observed, suggesting a competitive nature for this interaction as well. Thus the anti-idiotype behaves as a true beta-adrenergic antagonist, competing with both agonists and antagonists for the receptor site. The obvious potential uses of such receptor-specific antibodies are: the recognition of structural differences among subsets of beta-adrenergic receptors[28]; a more rigorous examination of their respective physiological role using reagents of greater resolution; and the isolation of receptors with antibody affinity chromatography.

Imaging of myocardial infarcts using cardiac myosin-specific antibodies

The hallmark of cell death is loss of the membrane integrity: when there is no longer a physical separation between inside and outside, the cell ceases to exist. This principle is commonly employed in clinical practice in diagnosing tissue infarction. Intracellular enzymes are lost to extracellular fluid, and their increased concentration in the blood may be used as a measure of tissue necrosis. An alternative approach is the inward diffusion of a marker that is normally excluded from cells. We have selected myocardial infarction as a model and radioactively labelled myosin-specific antibody as a marker.

Myosin is the principal protein of the cardiac cell. Its covalent structure is unique to the heart,[29] allowing the development of antibodies that differentiate between cardiac and either skeletal- or smooth-muscle myosins. In the intact organism, cardiac myosin is protected from extracellular fluid by the cell's plasma membrane. When cell death occurs and the membrane breaks down, myosin is exposed to extracellular fluid. It is then available to react with labelled antibodies or antibody fragments.

A visual demonstration of this phenomenon is seen in Fig. 4. The figure shows a scanning electron micrograph of part of a neonatal mouse cardiac myosite that had been rendered ischaemic by prolonged exposure to nitrogen and then incubated with $1\ \mu$ diameter, polystyrene spheres covalently bound to myosin-specific antibody. Myofibrils are seen protruding from a hole in the cell membrane. Antibody-coated microspheres clearly bind to the myofibrils. Not only is myosin very insoluble in physiological fluids so that membrane breakdown does not result in antigen loss, but it persists for considerable periods after ischaemic necrosis.[30] This should allow for identification of infarcted myocardium in days to, perhaps, several weeks after the initial event. In our initial exploration of this concept, a canine myocardial infarction model was used.[31] The left anterior descending coronary artery was ligated, and four hours later ^{125}I-labelled, myosin-specific antibody or antibody fragments were injected intravenously. At varying times after the injections, the animals were killed, the hearts were perfused with triphenyltetrazolium chloride, and the myocardia examined.[32] Fig. 5 (left) shows a section of a heart treated in this way. The light area represents a largely subendocardial infarction. The central panel of the figure is a tracing of the slice superimposed on an autoradiograph. The exposed area corresponds to the infarct as disclosed by the triphenyltetrazolium stain. The right panel shows specific radioactivity in the area of the infarct relative to myocardium on the posterior wall. It is apparent that the major concentra-

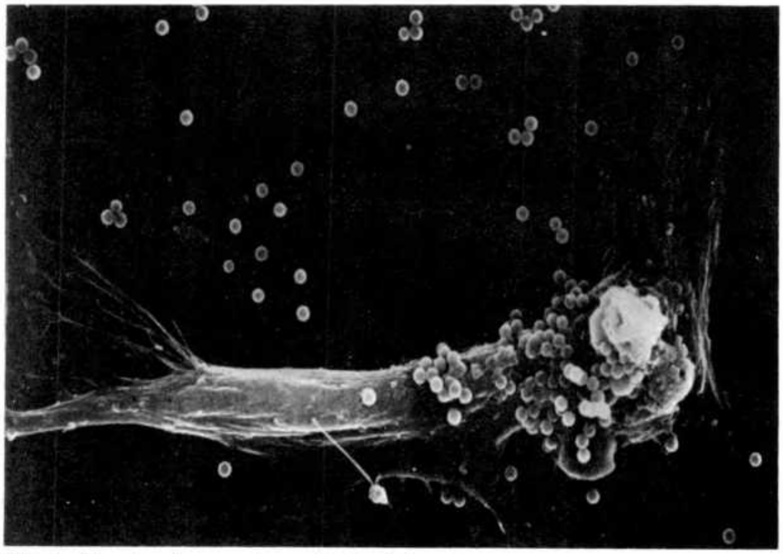

Fig. 4 *Scanning electron micrograph of an ischaemic neonatal mouse myosite (magnification × 2400). The spheres adherent to the cell are covalently bonded to myosin-specific antibody. Non-ischaemic cells do not bind significant numbers of spheres.*

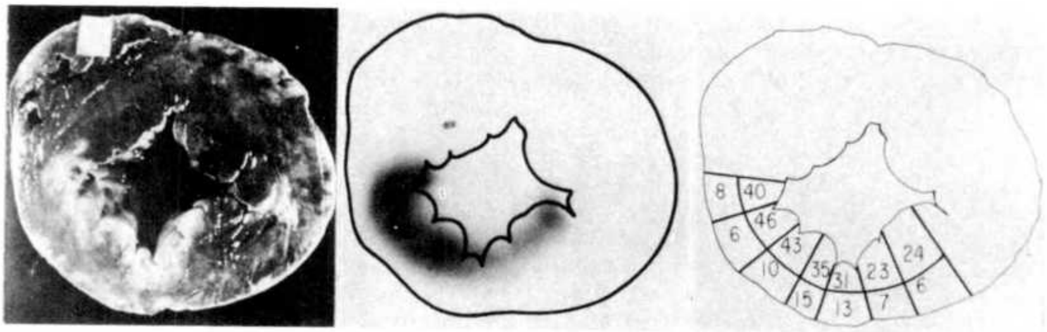

Fig. 5 *Histochemically delineated myocardial infarction in a ventricular slide (left) seen as white or lighter-coloured regions, and normal myocardium seen as darker regions. The corresponding macroautoradiograph is shown in the centre with the outline of the ventricular slide. The right panel shows relative antibody uptake in the indicated areas. Ratios of antibody uptake were determined as specific radioactivity in relation to normal posterior ventricular myocardium. (Reprinted with permission of the American Heart Association, Inc.* Proc N Engl Cardiovasc Soc *1979: Vol. II; 31–8.)*

tion of radioactivity is in the subendocardial region, with lesser concentration in the subepicardial region that had been subject only to spotty necrosis as indicated in the triphenyltetrazolium stain.

Microautoradiographs showed that individual necrotic myosites could be identified and differentiated from adjacent viable cells.[33] In order to show that antibody concentration was specific and not simply the result of passive diffusion of a macromolecule into infarcted cells, specific antibody labelled with ^{131}I and nonimmune globulin labelled with ^{125}I were injected simultaneously into the coronary arteries.[32] At the centre of the infarct, the antibody has concentrated 34-fold in relation to normal myocardium, while the nonimmune globulin is only sevenfold in excess. In normal tissue, as expected, concentrations are equal. When compared to a marker of relative flow, the distribution of radioactive microspheres which had been injected into the left atrium, it was clear that the concentration of labelled antibody was inversely related to relative blood flow.[31 32] There seems to be sufficient collateral circulation in this ischaemic model to provide for delivery of antibody, even to the regions of minimal blood flow. It would be very desirable to apply this method to the detection, localisation, and quantification of myocardial infarcts in the living subject.

Optimal imaging with a gamma or positron camera requires the labelling of antibodies with radionuclides of appropriate half-life and affinity. We have accomplished this by covalently linking diethylene triamine penta-acetic acid (DTPA) to antibody or antibody fragment and then binding cationic radionuclides by chelation.[34] Successful images have been obtained using the following radionuclides linked to antibody: ^{111}In-DTPA-Ab Fab,[34] ^{68}Ga-DTPA Fab,[35] and ^{99m}Tc-DTPA-Ab Fab.[34] An example of a positron image of an anterior infarct in a living dog using ^{68}Ga-labelled antibody is shown in Fig. 6 (left). The positron imaging technique allows for tomographic reconstruction and, thus, the heart is visible on cross-section in the ^{13}N-ammonia image in the centre panel of Fig. 6 (ammonium ion is a potassium analogue and concentrates in normal tissue). On the left side of the image there is clearly less density, reflecting the region of infarction. Superimposition of the ^{13}N and the ^{68}Ga images (right panel) showed that the antibody was concentrated directly in the area of diminished ammonium ion uptake. The potential for applying this method to the evaluation of myocardial infarcts in a clinical setting seems very great indeed since it offers high specificity and resolution.

Reversal of digitalis glycoside intoxication

If the effect of an endogenously produced hormone can be reversed, it should also be possible to counteract the undesirable effects of an exogenously administered drug or toxin. The digitalis glycosides are of great value in the treatment of congestive heart failure and consequently are frequently used in clinical medicine. Unfortunately, they are characterised by a very close toxic-therapeutic ratio. Digitalis intoxication is one of the most frequent adverse drug reactions reported. There is no specific antidote, and the cardiac arrhythmias that are a feature of digitalis intoxication are not uncommonly fatal.

We reasoned that if an antibody specific to the digitalis glycosides had a higher affinity for the drug than the physiological receptor, it should be possible to transfer the ligand from the receptor to antibody, simply by mass action. For optimal effectiveness diffusion distances should be minimal, and the antibody should be in high concentration in extracellular fluid in proximity to the receptor. It would also be desirable to remove the antibody-drug complex rapidly from the body. Both aims may be accomplished by the use of digitalis-specific Fab. As indicated above, the volume of distribution of Fab is greater than intact antibody since it readily enters extracellular fluid. It is also of sufficiently small size (50 000 Daltons) to pass through the glomerular filter and be largely excreted in the urine.[36]

Digoxin-specific antibody was purified from sheep antiserum using immobilised ouabain Fab isolated after papain cleavage.[37] After demonstration of safety and effectiveness in animal studies, clinical investigations were initiated. At the time of this writing, 17 patients with life-threatening digitalis intoxication have been studied. The patients ranged in age from

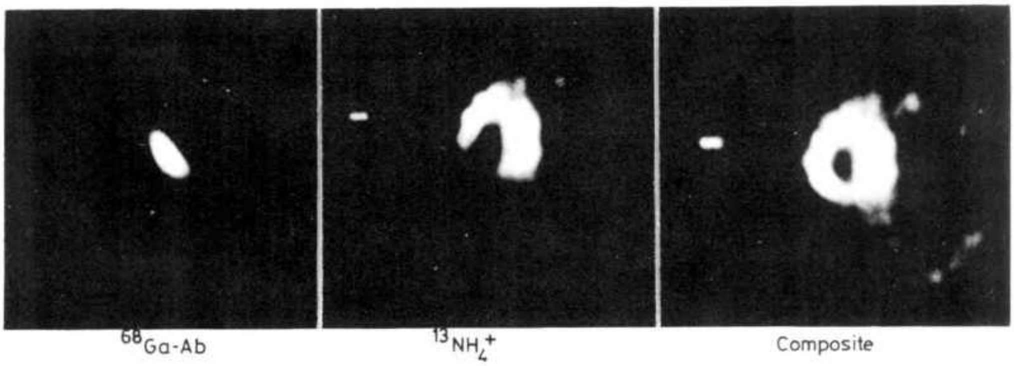

Fig. 6 *^{68}Ga and $^{13}NH_4^+$ were obtained sequentially using a positron camera; 5 mCi of $^{13}NH_4^+$ was administered intravenously to a dog that had had occlusion of the distal segment of the left anterior descending artery for four hours and was imaged (centre); 30 minutes later 1 mCi of ^{68}Ga was injected into the same artery and imaged (left panel). Right panel is a composite of both images. (Reprinted with permission of the American Heart Association, Inc.* Proc N Engl Cardiovasc Soc *1979: Vol. II; 31–8.)*

infants to septuagenarians and in each case a dramatic reversal of the signs and symptoms of intoxication occurred.[38–40]

The history of a recently reported patient is typical of the group.[39] She was a 34-year-old wife of a physician, who, because of marital difficulties, took 20 mg digitoxin, a massive overdose. She appeared well on admission to the hospital except for nausea, but soon lapsed into a series of life-threatening arrhythmias that included multiple episodes of ventricular fibrillation, which were treated with countershock, as well as asystole, which was treated by ventricular pacing. At the time the antibody Fab became available to the physicians treating her, the patient was in shock and anuric, and she had dilated pupils. Her serum potassium was raised, a grave prognostic sign in digitalis intoxication.[41] Within an hour after the intravenous administration of antibody Fab, her atrioventricular conduction had returned, and she was soon in normal sinus rhythm. No further arrhythmias occurred. She was discharged from hospital without sequelae several days later. Fig. 7 shows the initial distinct increase of serum digitoxin concentration in this patient as tissue-bound drug equilibrated with the antibody (antibody-bound drug is pharmacologically inactive), followed by rapid clearance of both drug and Fab. It should be noted that the half-life of digitoxin in man is normally three and a half days when hepatic metabolism of the drug is the major source of removal. It is apparent that excretion was much accelerated by the antibody Fab, the half-life apparently reduced to about 12 hours. Fig. 8 shows that both antibody and Fab appear in the urine in largest amounts within the first day after Fab administration.

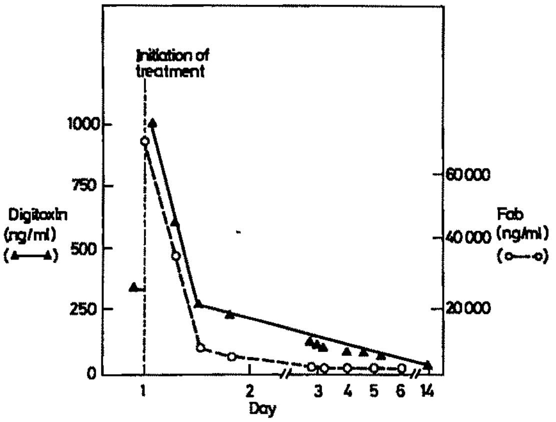

Fig. 7 *Blood levels of digitoxin and Fab after intravenous administration of antibody Fab to a 34-year-old woman suffering a series of life-threatening arrhythmias as a result of a massive overdose (20 mg) of digitoxin. Within an hour of intravenous administration of antibody Fab, atrioventricular conduction had returned. (Reprinted from* Contributions of chemical biology to the biomedical sciences *with permission of Academic Press, New York. In press, 1981.)*

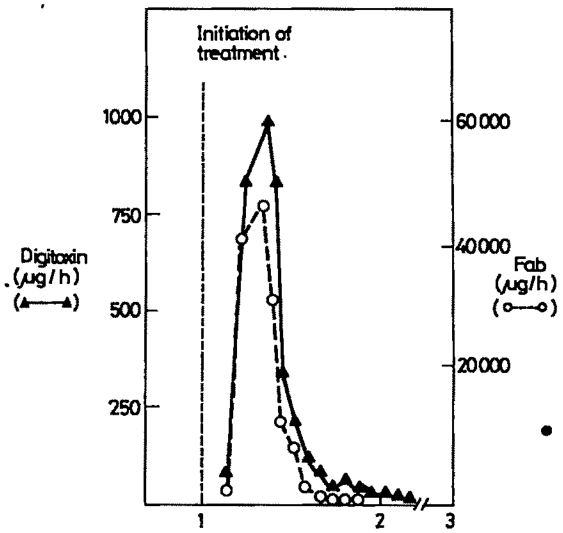

Fig. 8 *Urinary excretion rates of digitoxin and Fab after intravenous administration of antibody Fab to a 34-year-old woman suffering from digitalis intoxication (20 mg). (Reprinted from* Contributions of chemical biology to the biomedical sciences *with permission of Academic Press, New York. In press, 1981).*

The digitalis glycosides in most common use are digoxin and digitoxin. They differ from one another very little in their chemical structure, yet most antibodies differentiate between them, with differences in affinity of 50- to 100-fold.[2] It would be desirable to use an antibody that bound both digoxin and digitoxin with equal affinity. A monoclonal antibody (designated 26-10 in our laboratory) was selected that had an affinity of 5×10^9 for digoxin and a nearly equal affinity for digitoxin.[42] Since a monoclonal antibody is a homogeneous protein that recognises only a single aspect of an antigen molecule, it appears that the hydroxyl group is not a part of the antigenic recognition site of this molecule. This antibody, which can be produced in quantities without limit, has been shown to reverse digoxin intoxication in experimental animals.

It should be apparent that this approach could be applied to many other drugs or toxins. Of particular interest is the acceleration of excretion of a substance that is normally metabolised slowly. Fab is capable of altering the route of disposal from hepatic metabolism to renal excretion.[43]

Antibodies as drugs

The development of a new drug is often the result of empiricism, serendipity, or the deliberate modification of an existing natural product. These products of the organic chemist's laboratory are usually characterised by a lack of specificity with consequent abundance of adverse reactions. If antibodies were the basis of identification of a specific site within the body for binding, blockade, or modification, one could choose among some 10^{11} different recognition sites and thus much increase specificity. Adverse reactions to drugs are most often the result of reaction with a site other than the desired target. Selective interaction should, of necessity, diminish these undesired effects. The considerably larger size of the antibody combining site in comparison to conventional drugs allows for the establishment of a greater number of specific interactions among atoms and thus both greater affinity and specificity.

While some of the advantages of antibodies are obvious, the disadvantages, discussed in part above, must also be considered. When binding to a specific site is all that is desired, the activation of the biological effects that are an intrinsic part of an immune reaction is undesirable. The smaller Fab that was discussed above as a possible solution to some of these problems still carries with it an entire domain (one half of its mass) that is of no relevance to antigen binding. Fab from a heterologous species, while of diminished immunogenicity, is likely to cause hypersensitivity when used on a long-term basis. The solutions to these problems are almost at hand. A much smaller fragment of antibody has been produced that retains all the binding energy and specificity of the intact molecule. Fv comprises a single domain and has a molecular size of 25 000 Daltons.[44] While its pharmacokinetics have not as yet been examined, I anticipate that it will be very rapidly cleared and distributed. The advent of the hybridoma method will make possible not only the selection and large-scale production of antibodies of uniform properties, but also the reduction or elimination of the potential problem of hypersensitivity, since it will be possible, as indicated above, to produce human antibodies. Will the formation of anti-idiotypic antibodies defeat the long-term utility of antibody therapy? I believe that the well-recognised difficulty in producing anti-idiotypes, even deliberately, indicates that this problem will be rare. The next decade will see a new pharmacology based on the antibody combining site.

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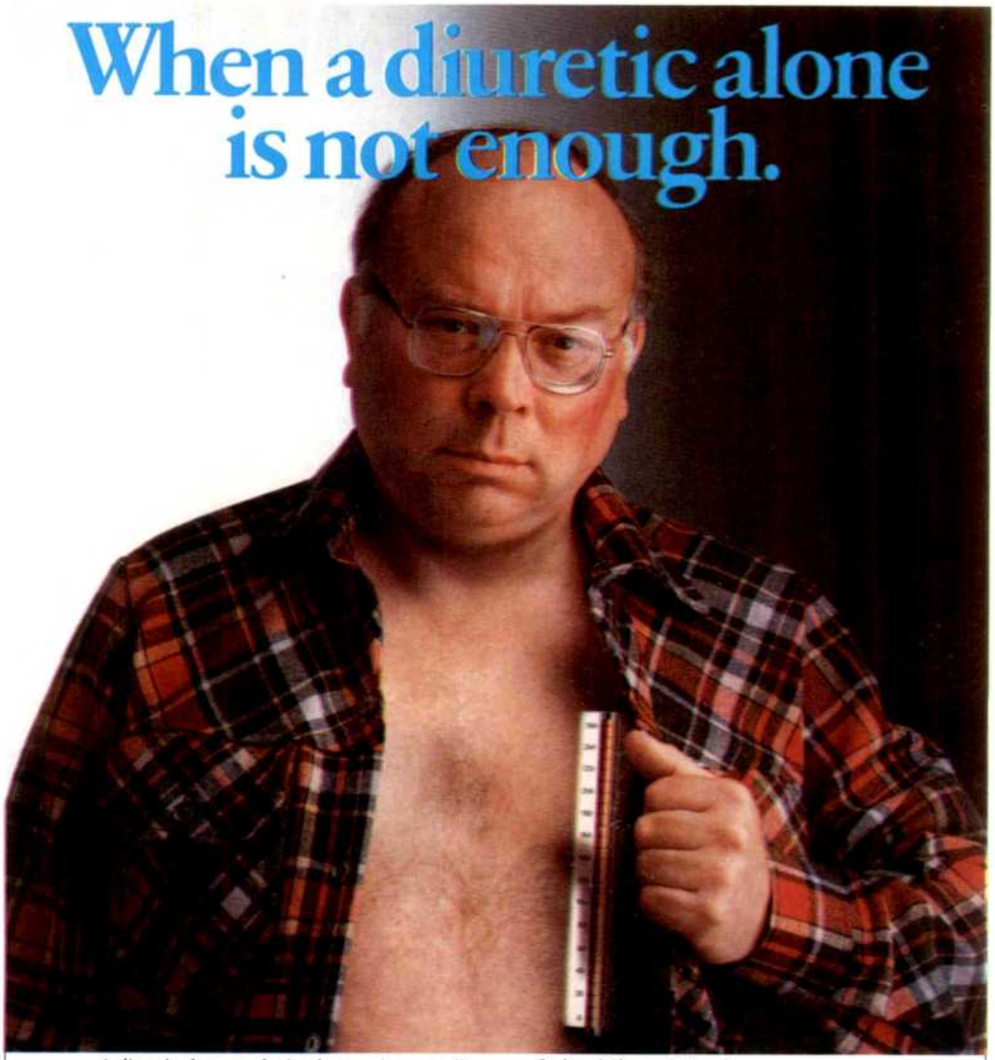

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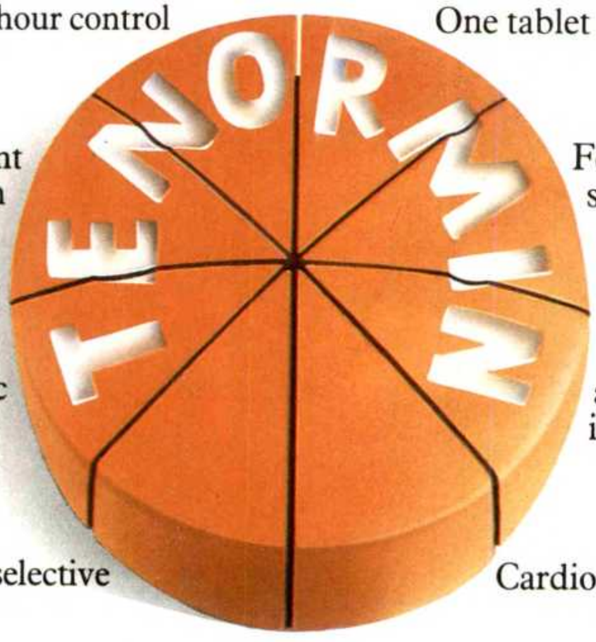

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Assessment of heart neurons in dilated (congestive) cardiomyopathy

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SUMMARY Pathological studies in seven hearts from patients with dilated cardiomyopathy have shown that the number of neurons is significantly reduced in these compared with five hearts from normal subjects. The number of ganglion cells was counted in a strip of right atrial wall between the venae cavae and sectioned serially.

The mechanism responsible for the neuronal depopulation in this stype of cardiomyopathy could not be determined. Previous viral infection may be causally related. Three hearts of patients suffering from chronic Chagas's heart disease were also studied. Depopulation of neurons was most severe in the hearts with Chagas's disease and less severe in those with dilated cardiomyopathy, though neurons were still significantly reduced in number in the latter compared with normal controls.

Despite the lack of a specific, definite cause for the depopulation of neurons, physiological evidence of parasympathetic impairment in patients with dilated cardiomyopathy is in agreement with the pathological findings. It is suggested that on the basis of our findings neuronal depopulation in some patients with dilated cardiomyopathy may be of aetiological significance.

Dilated (congestive) cardiomyopathy is characterised by ventricular failure of no detectable cause and the possibility of a multifactorial aetiology has been entertained.[1 2] In this clinical entity physiological investigations indicate that even at an early stage of the disease parasympathetic function is impaired,[3] as in patients with chronic Chagas's heart disease.

In the latter condition pathological observations have consistently shown neuronal destruction at subepicardial level and lesions in the cardiac nerves.[4 5] In normal sized hearts of these patients, physiological investigations showed abnormal heart rate responses, interpreted as an indication of neuronal degeneration in the sinuatrial region.[6]

In view of the physiological findings in patients with dilated cardiomyopathy, seven hearts from patients in whom a firm diagnosis of this condition had been made during life have been examined and compared with five hearts obtained from subjects who had died from extracardiac causes. These findings were compared with three hearts from patients with chronic Chagas's heart disease.

Material and methods

Seven hearts were used in this study from four men and three women whose mean age was 41·5 years ±7·1 (standard error, SE) who had died from dilated cardiomyopathy and in whom complete clinical data and detailed necropsy findings were available. The clinical diagnosis was made according to accepted criteria.[7] In addition three hearts, all male, with chronic Chagas's disease, mean age 45·6 years ±8·1 (SE) were used for comparison. Five hearts from individuals having died as a result of road traffic accidents served as controls; they were all men, mean age 44·4 years ±6·0 (SE).

A technique, previously described,[4] was employed to assess the number of ganglion cells. A rectangular block of tissue selected from the posterolateral wall of the right atrium between the venae cavae was removed. This strip was divided into four blocks, all marked to ensure correct sequential orientation. The blocks were paraffin embedded and 7 μm thick sections were cut serially. Every seventh section was stained with haematoxylin and eosin and intervening random sections were stained with Miller's elastic van Gieson stain for assessment of collagen tissue. The sections were examined and analysed under light microscopy but

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Table 1 *Clinical findings in patients with dilated hypertrophy*

Case no.	*Sex*	*Age (y)*	*Duration symptoms (mth)*	*Heart failure*	*Physical findings*	*Blood pressure (mmHg)*	*Electrocardiogram*
1	M	21	9	+	Gallop rhythm	110/60	ST, LVH
2	M	43	57	+	Gallop rhythm SM (MA)	120/90	ST, LBBB
3	F	35	84	+	Split P_2 SM (MA)	110/70	SR, EAF, LAHB, LQRS
4	F	67	48	+	Gallop rhythm SM (MA)	120/90	ST, LVH
5	F	62	18	+	SM (MA)	120/80	ST, FAV, LBBB
6	M	16	3	+	SM (MA) (AA)	120/80	W
7	M	47	6	+	Gallop rhythm	120/70	ST, LVH

EAF, episodes of atrial fibrillation; FAV, first degree atrioventricular block; LAHB, left anterior hemiblock; LBBB, left bundle-branch block; LQRS, low voltage QRS complex; LVH, left ventricular hypertrophy; P_2, second pulmonary sound; SM, soft systolic murmur at MA (mitral area) or AA (aortic area); SR, sinus rhythm; ST, sinus tachycardia; W, atypical Wenckebach type I block.

Table 2 *Pathological findings in hearts with dilated hypertrophy*

Case no.	*Heart weight (g)*	*RA (mm)*	*RV (mm)*	*LA (mm)*	*LV (mm)*	*TV (cm^2)*	*PV (cm^2)*	*MV (cm^2)*	*AV (cm^2)*	*RD length (mm)*	*No. of Neurons*
1	510	2	5	2	12	140	80	120	70	32	7040
2	680	4	9	4	15	140	95	115	80	30	5084
3	430	3	3	2	13	130	72	—	68	32	4494
4	590	2	4	3	15	125	75	100	70	39	4464
5	495	2	5	3	13	125	80	95	70	45	4006
6	320	1	5	—	13	110	63	92	55	33	3585
7	570	3	6	3	16	130	82	105	75	36	3281

AV, aortic valve; LA, left atrium; LV, left ventricle; MV, mitral valve; PV, pulmonary valve; RA, right atrium; RV, right ventricle; TV tricuspid valve; RD length, strip of the right atrium removed from the posterolateral wall for ganglion cell count.

for assessment for the size of neurons a Projectina microscope (Model 4014, Optical Works Ltd) was used. Particular attention was paid to the number of ganglion cells, to the amount of collagen tissue, and to whether or not an inflammatory infiltrate was present.

The margin of error in counting ganglion cells was assessed by determinations made by two independent observers. The statistical analysis was based on unpaired tests of significance.

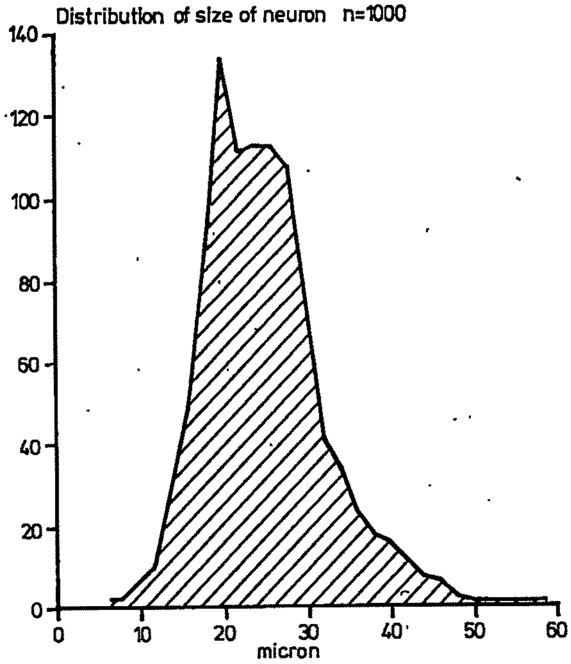

Fig. 1 *Determination of neuronal size. The size of 1000 cells, sampled from the three groups of hearts, was measured in detail by means of the Projectina microscope.*

Results

Clinical data and macroscopical pathological findings of patients with dilated cardiomyopathy are summarised in Tables 1 and 2.

LENGTH OF ATRIAL TISSUE

In control hearts the length of the right atrial strip averaged 35·8±2·7 mm (SE) while in dilated cardiomyopathy and hearts with Chagas's disease it averaged 35·2±1·0 and 29·6±6·6 mm (SE), respectively.

DETERMINATION OF NEURONAL SIZE

In order to ensure that neuronal cells were not counted twice, the size of 1000 cells, sampled from the three groups, was measured in detail. Results are shown in Fig. 1. It can be seen that the larger diameter averaged 24·8 ± 0·22 μ (SE). In only three of the 1000 cells did the diameter equal or exceed 50 μ (50, 52, and 58 μ), the results being obtained by direct measurement.

GANGLION: NUMBER OF CELLS AND STRUCTURE

A ganglion cell was considered normal if the integrity of the cell wall was intact and the cell was embedded in a delicate framework of collagen tissue, in the absence of inflammatory cells (Fig. 2A & B). In contrast, when prominent collagen tissue was present, replacing the cells to a varying degree, it was deemed abnormal (Fig. 3A & B). Inflammatory cells, as seen in hearts with Chagas's disease (Fig. 4), were not encountered in the hearts from patients with dilated cardiomyopathy.

In the control hearts the neuronal count averaged 6412 ± 377 (SE), the range being from 5180 to 7511

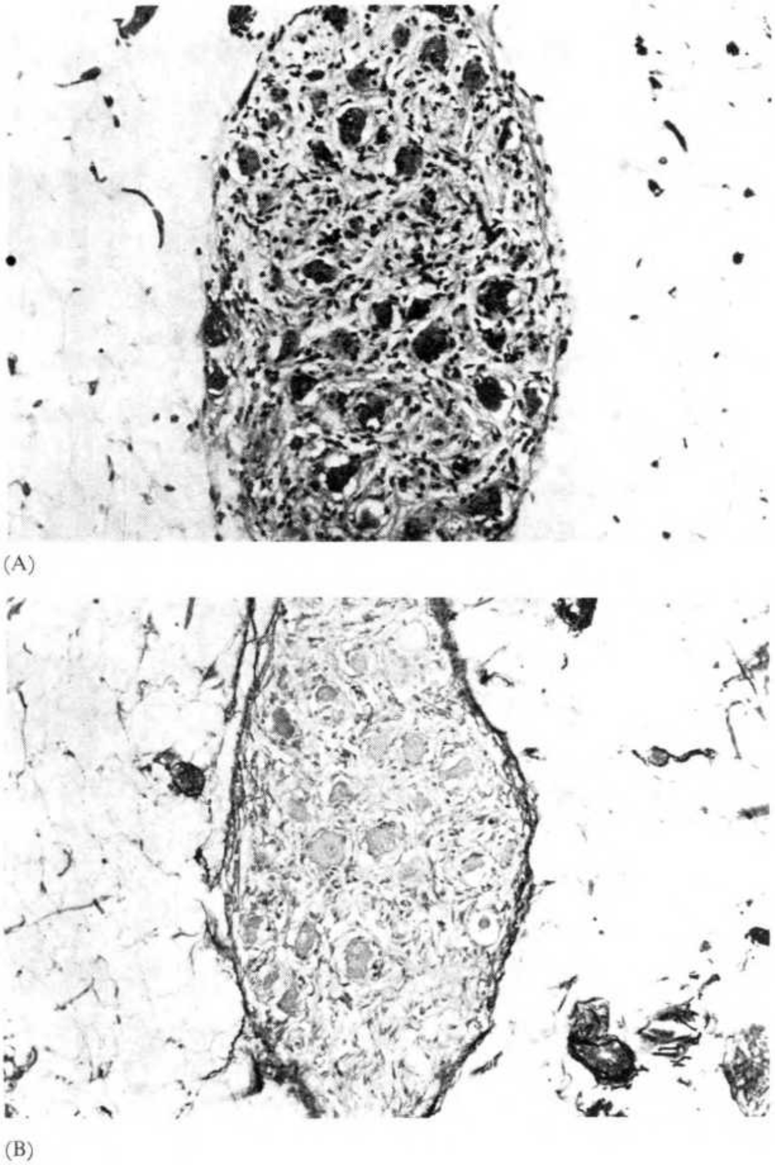

Fig. 2(A) *A normal ganglion with an evenly distributed neuronal population. (Haematoxylin and eosin. × 200 original magnification.)* (B) *The neurons are embedded in a delicate framework of collagen tissue. (Miller's elastic van Gieson. × 200 original magnification.)*

neurons. In contrast, in the hearts with dilated cardiomyopathy the number of neuron cells was significantly reduced. The average count obtained was 4565 ± 471 (SE), the range being from 3281 to 7040 neurons ($p < 0{\cdot}002$). The values for each heart are detailed in Fig. 5. It can be seen that in six out of the seven hearts the number of ganglion cells was below the lowest value obtained in the control group.

The neuronal count in hearts with Chagas's disease showed a striking reduction, with values as low as 492, 543, and 1286 in the three hearts examined.

In order to avoid a possible source of difference in the number of ganglion cells counted because of the length of the right atrial tissue examined, we calculated the number of cells per millimetre of tissue (Fig. 6). Results showed that in the control hearts an average number of 184 ± 16·5 (SE) was obtained, whereas 131 ± 17·3 (SE) was found in

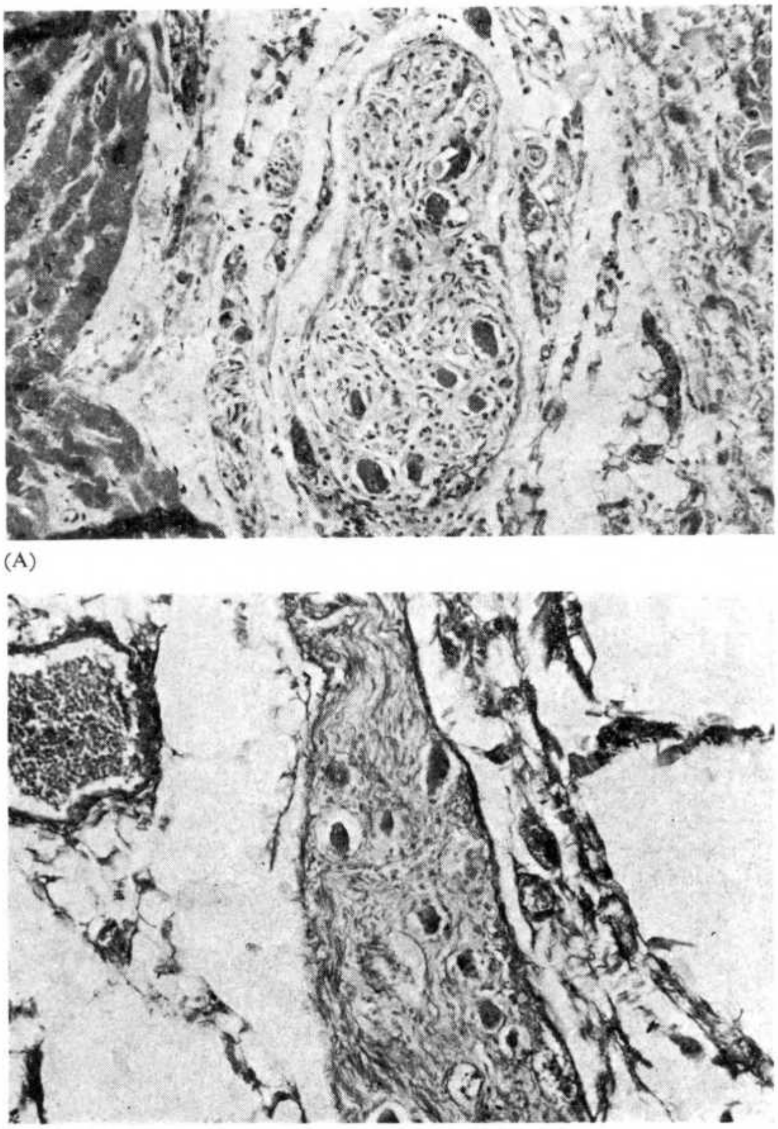

Fig. 3(A) *Photomicrograph of a ganglion from a patient with dilated cardiomyopathy. Note the depopulation and uneven distribution of neuronal cells. (Haematoxylin and eosin. × 200 original magnification.)*
(B) *Part of a ganglion from a patient with dilated cardiomyopathy showing extensive replacement of the neuronal cells by collagen tissue. (Miller's elastic van Gieson. × 200 original magnification.)*

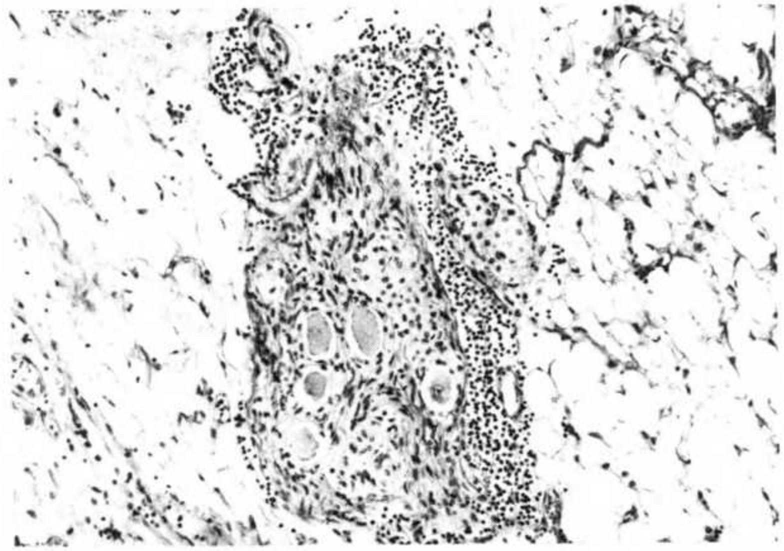

Fig. 4 *Ganglion from a patient with chronic Chagas's heart disease. Severe depopulation of neurons is present. Note also the chronic inflammatory infiltrate. (Haematoxylin and eosin. × 200 original magnification.)*

hearts with dilated cardiomyopathy ($p < 0{\cdot}05$). As can be seen in Fig. 6, in five of the seven hearts, the number of cells per millimetre of tissue was below 1 standard deviation (SD) of the mean value obtained in the controls. In hearts with dilated cardiomyopathy no correlation could be found between the neuronal counts and age, duration of symptoms, heart weight, and wall thickness. Extremely low values in the number of ganglion cells per millimetre of tissue were obtained in all the three hearts with chronic Chagas's disease (Fig. 6).

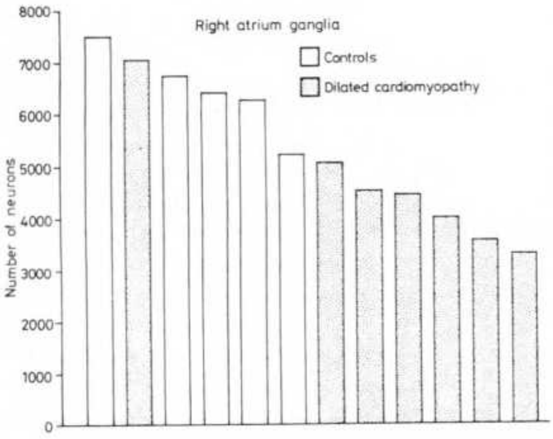

Fig. 5 *Number of ganglion cells counted in a strip of the right atrial wall between the venae cavae. In hearts with dilated cardiomyopathy the number of neuron cells was significantly reduced* ($p < 0{\cdot}002$).

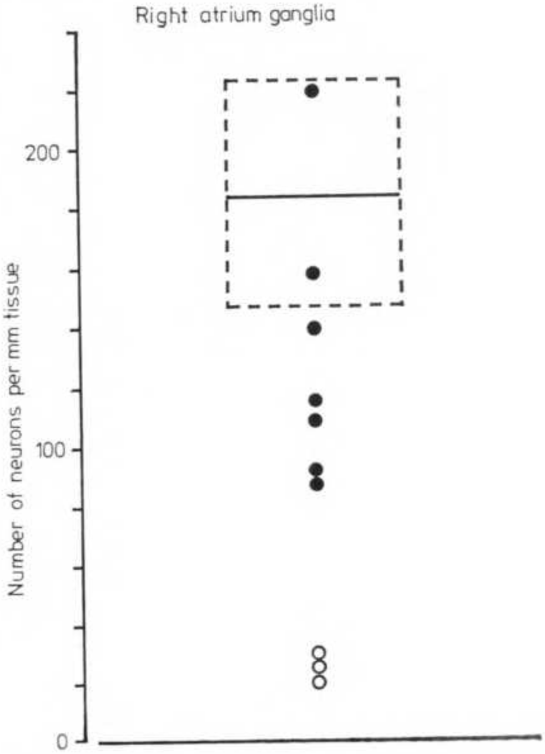

Fig. 6 *Number of ganglion cells per millimetre of right atrial tissue. The complete and dashed lines represent the average value and standard deviation of control hearts. Five hearts with dilated cardiomyopathy (solid circles) present a value less than 1 SD, while in all three hearts with Chagas's disease (clear circles) extremely low values were obtained.*

Thus, compared with the controls, the morphological abnormalities in dilated cardiomyopathy were, in particular, the amount of collagen tissue present and a severe degree of neuronal depletion.

Discussion

The diagnosis of dilated cardiomyopathy was made according to established criteria.[7] Left ventricular hypertrophy and left bundle-branch block were common (Table 1) and these, together with severe electron microscopical changes, indicate a poor prognosis.[8]

Though several factors have been suggested as being causative of or contributory to this type of cardiomyopathy the aetiology or aetiologies are so far unknown.[1]

The three patients with Chagas's heart disease presented with enlargement of the heart and clinical manifestations of heart failure lasting from six to 12 months. Impaired autonomic function has been reported in heart failure.[9] [10] These changes probably occur as a direct result of a poor cardiac output and are therefore non-specific, heart failure being associated with a deficit of cardiac noradrenaline and a deficiency of sympathetic function.[9] For defective cardiac parasympathetic control no satisfactory explanation has been offered.[10] Recently we have studied patients with dilated cardiomyopathy who had a slight degree of cardiac enlargement and no recorded clinical manifestations of overt heart failure. These patients had abnormal heart rate responses during isometric exercise, impaired baroreflex sensitivity, and diminished cardiac acceleration in response to atropine-induced withdrawal of parasympathetic restraint.[3] Defective parasympathetic control has previously been reported in patients with chronic cardiac Chagas's disease who had no cardiac enlargement and no clinical or functional evidence of cardiac failure.[6]

We undertook this study in view of the similarity of the pathological and functional derangements of autonomic control in Chagas's disease and dilated cardiomyopathy.

The technique we have used ensured that no neuron was counted more than once. Our determination of neuronal size validates this basic requirement and renders any possible error negligible (Fig. 1). Furthermore, the margin of error in the number of cells was very small, because ganglion cell counts by two independent observers showed 97 per cent agreement.

Though there might be differences in cell count between different laboratories depending on the method used, these are minor and never of the order of those found between the control hearts and those with dilated cardiomyopathy. The number of ganglion cells in the cases of dilated cardiomyopathy was not reduced as severely as in the hearts with Chagas's disease but was significantly reduced in comparison with normal controls.

It could be argued that the length of atrial strips could influence the neuronal count. We have shown that this was not the case.

Macroscopically (Table 2) and histologically the accepted non-specific changes of dilated cardiomyopathy were found.[2] These differ from those in Chagas's heart disease in which thinning of the cardiac wall at the apex ("apical aneurysm"), diffuse interstitial fibrosis, and focal myocarditis are typical. The inflammatory cells frequently present in the heart ganglia in Chagas's disease (Fig. 4) were in striking contrast to hearts with dilated cardiomyopathy, in which inflammatory cells were never seen.

The mechanism of neuronal cell destruction remains undetermined. Perhaps neuronal depopulation is an accompaniment of heart failure. It could thus occur in heart disease of known aetiology such as rheumatic heart disease.

It is tempting to speculate that neuronal depletion is aetiologically related to dilated cardiomyopathy. Further studies are necessary before such a supposition can be conclusively proved.

In Chagas's heart disease degenerative lesions of the heart ganglia are well known in man as well as being found in experimental infection with *Trypanosoma cruzi*.[4] [6] Comparative studies have shown an average of 4500 neurons in normal human hearts and an average of 739 (ranging from 0 to 3316) in 51 cases with chronic Chagas's heart disease.[4] Studies have also been undertaken in endomyocardial fibrosis (five cases) and in "idiopathic cardiomegaly" (nine cases),[11] a label, however, which included diverse diagnoses. Unfortunately, neither clinical data nor the duration of the illness were stated and therefore interpretation of the results is difficult. It has been suggested that in Chagas's disease neuronal destruction is produced by *T. cruzi* antigens which render lymphocytes cytotoxic to ganglion cells and that delayed hypersensitivity may be the mechanism responsible for cell destruction.[12] Sera of patients with chronic Chagas's disease contain antineuron antibodies and it has been further suggested that in chronic infections the continuous liberation of autoantigens from injured tissue may be the stimulus for the perpetuation of the autoimmune response.[13]

It is possible that in dilated cardiomyopathy a cell-mediated immune response related to an initial viral infection may exist and be causally related to neuronal depopulation. Cambridge *et al.*[14] showed antibodies to Coxsackie B virus in some patients with dilated cardiomyopathy. Furthermore, there is evidence that in mice infected with Coxsackie B viruses an immune response develops with production of cytotoxic T cells which can damage tissues infected with virus.[15] At present the immunological implications are ill-understood and further work is necessary to establish clearly a causal relation, but in some heart diseases (for example Chagas's disease[16] and congestive cardiomyopathy[17]) there appears to be an association with immunoglobulin binding of the myocardium, and the presence of antiheart antibodies in patients' sera.

The motor nucleus of the vagus supplies preganglionic fibres which are distributed to the epicardial ganglia.[18] In man, ganglion cells in the heart are only found subepicardially in the atria, forming a plexus. From this plexus, both myelinated and non-myelinated fibres enter the heart wall, where they intermingle extensively. In our studies we have not examined the length and distribution of these fibres in the tissues of the heart, but have concentrated on the subepicardial ganglion cells.

The influence of the parasympathetic nerves on the sinuatrial node is well known, but there has been considerable controversy regarding the inotropic effect on ventricular muscle.[19] It has been shown that on stimulating the vagal nerves at constant heart rate there is only a very small negative inotropic effect on the ventricle.[20] This effect is debatable, however, and it would be interesting to explore the consequences of impairment of parasympathetic function, because the ability to alter heart rate is an important mechanism in the adjustment of cardiac output.

Our physiological findings[3] show that in dilated cardiomyopathy even at an early (prefailure) stage parasympathetic function is impaired and not associated with a significant increase in sympathetic activity. These patients, therefore, may be deprived of this sensitive mechanism for effecting rapid changes in heart rate.

Thus, we conclude that neuronal depopulation is linked with evidence of parasympathetic dysfunction in dilated cardiomyopathy. Though it has, so far, not been possible to determine the cause of neuronal degeneration in this disease, the physiological findings have a functional relevance.

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Interrelation of heart rate and autonomic activity in asymptomatic men with unobstructed coronary arteries

Studies with atrial pacing, adrenaline infusion, and autonomic blockade

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SUMMARY We have extended our observations on asymptomatic men with abnormal resting electrocardiograms showing changes indistinguishable from those of myocardial ischaemia but with normal coronary arteriograms. In the present investigation we aimed to separate the effects of heart rate alone from those of the sympathetic nervous system. We therefore studied the effects of atrial pacing alone, pacing and adrenaline infusion combined, pacing after beta-blockade, and pacing after beta-blockade plus atropine.

Twenty asymptomatic men, aged 17 to 57, were investigated. All were shown to have unobstructed coronary arteries and normal left ventricular angiograms. Echocardiographic findings were normal. Sixteen had flat or inverted T waves in the lateral leads (designated "T"), two had ST depression (designated "ST"), and two had mixed patterns.

T wave abnormalities and, to a lesser extent, ST changes returned to normal or regressed after an overnight rest in hospital. Subsequent atrial pacing to 160/minute reproduced or increased the respective abnormalities. When adrenaline was infused in low doses just sufficient to produce discernible effects on the ST-T segment (between 0·024 and 0·091 μg/kg per min) and atrial pacing was repeated, the effect of the latter was enhanced. Both adrenaline and pacing influenced the ST-T segment in the same direction. Intravenous propranolol (0·2 mg/kg) blocked the effect of adrenaline and its synergistic effect with pacing but exerted little if any influence on the effect of pacing alone. Atropine given intravenously after propranolol (0·04 mg/kg) reduced the effect of atrial pacing on the ST-T configuration.

Treadmill exercise tests were positive in nine and borderline in one. After beta-blockade (oral oxprenolol), all tests were negative. As beta-blockade did not prevent pacing-induced ST depression but normalised the false positive exercise test, the latter does not appear to be rate related but more probably the result of the direct influence of catecholamines. Isolated T wave changes and ST depression in the resting electrocardiogram differ in that they are influenced both by heart rate and catecholamines acting synergistically.

We have reported observations on asymptomatic men with abnormal electrocardiograms showing changes indistinguishable from those of myocardial ischaemia but with normal coronary arteriograms.[1] An altered response to autonomic activity was shown whereby these changes could be readily manipulated by measures designed to influence sympathetic activity, such as tranquillity, intravenous infusion of adrenaline, and beta-adrenergic blockade. Since changes in heart rate as well as sympathetic behaviour may be relevant, however, acting either independently or in combination, it seemed appropriate to attempt to evaluate the effect of each separately and the interplay between the two on the electrocardiographic configuration in a similar group of asymptomatic men.

We have accordingly recorded the electrocardiogram during atrial pacing, intravenous adrenaline infusion, and the combination of the two, both with-

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out medication and after propranolol and also after propranolol together with atropine. We have also included maximal treadmill exercise tests without medication and after oxprenolol to allow comparisons to be drawn between the ST-T changes induced during the above procedures and during exercise.

Subjects and methods

The subjects were 20 men aged 17 to 57 (mean 35) whose professional livelihood was threatened by abnormalities indistinguishable from those of myocardial ischaemia on a routine resting electrocardiogram. All were asymptomatic expect one, an 18-year-old with a mildly depressed sternum who presented with undue dyspnoea and tachycardia on exertion; these symptoms only occurred on that occasion, and he showed excellent effort tolerance on treadmill exercise testing. All the subjects were referred because of abnormal resting electrocardiograms. Physical examination disclosed nothing other than the depressed sternum described and mild hypertension in two individuals one of whom was taking a diuretic. None had the Wolff-Parkinson-White syndrome or other conditions known to be associated with a false positive exercise test. The nature and purpose of the tests were explained to each subject.

EXERCISE TESTING

Maximal treadmill exercise tests were carried out twice on each subject, before and one and a half hours after an oral dose of 80 mg oxprenolol. The multistage protocol of Bruce was adopted[2] using the Avionics monitor model 3000 with computer programmer P.100 and recording 3 CM leads positioned according to the praecordial leads showing the most conspicuous abnormalities. CM5 was included in each case. The end point chosen was fatigue and no test had to be terminated prematurely. Tests were classed as positive, negative, or borderline.[1]

ECHOCARDIOGRAMS

Echocardiograms were performed on all subjects using the Smith-Kline Echoline 20A and 2·25 transducer focused at 7·5 cm recording on a Cambridge fibreoptic recorder. The technique was as previously described[1] but a septal to posterior free left ventricular wall ratio of 1·3 rather than 1·5 was taken as the upper limit of normal.

CARDIAC CATHETERISATION

Left heart catheterisation and coronary angiography were carried out using the Sones or Judkins technique. Single plane left ventricular cineangiography was performed in the right anterior oblique position at 30° at 40 frames per second.

PACING/INFUSION STUDIES

A 5F bipolar pacing electrode was positioned in the high right atrium via the right femoral vein. Pacing was carried out with a 1 ms pulse width at twice the diastolic threshhold.

Freshly diluted adrenaline was infused into a left arm vein by a Harvard constant infusion pump (model 975) at four dosage rates: 0·024, 0·047, 0·091, and 0·18 μg/kg per min.

A three-channel electrocardiogram was recorded using the lead positions selected for the exercise tests.

The electrocardiogram was recorded for 10 seconds at a time; at rest and during atrial pacing at rates of 100, 120, 140, and 160 per min each, or to the highest rate where 1:1 atrioventricular conduction was achieved. Adrenaline was then infused for four minutes at the lowest dose rate and the electrocardiogram recorded before and during incremental atrial pacing. The infusion was then discontinued for three minutes before the next dose. In this way recordings reflected pacing alone, adrenaline alone, and the two in combination at different infusion rates. Higher doses were not used if a clear-cut effect was produced by a lower one.

In 10 patients propranolol was then administered intravenously (0·2 mg/kg) and the procedure was repeated using the highest dosage of adrenaline that had been administered. These 10 patients were then given intravenous atropine (0·04 mg/kg) and pacing was repeated without adrenaline infusion.

Results

RESTING ELECTROCARDIOGRAMS

Sixteen subjects showed flat or inverted T waves in either the inferolateral or anterolateral leads in their resting electrocardiogram, two had ST segment depression, and two had mixed patterns (Table).

ECHOCARDIOGRAMS

No subject with any echocardiographic abnormality was included in the study.

EXERCISE TESTS

Treadmill tests fulfilled the criteria as positive for myocardial ischaemia in nine, they were borderline in one, and negative in 10 when conducted without medication. When repeated after oxprenolol they were negative in all 20. Of the nine positive tests before oxprenolol, five were already positive and two were borderline at a fairly early stage when the heart rate had reached the maximum rate achieved during the tests on oxprenolol (Table). Maximum heart rates without medication and after oxprenolol were 184 ± 12·8 and 130 ± 11·9, respectively.

One subject, case 9, had a positive test both before

Table *Individual data on 20 subjects in study*

Case No.	*Age (y)*	*Electrocardiogram*	*Treadmill exercise*			*Pacing/infusion*	
			No medication MHR	*At MHR blocked*	*Oxprenolol MHR*		
1	53	ST	150 +	–	100 –		↓
2	52	ST	190 +	+	125 –		↓
3	18	T	170 –	–	130 –	↓	
4	17	T	180 –	–	130 –	↓	
5	28	T	190 +	B	110 –	↓	
6	42	T	180 –t	–	130 –	↓	
7	43	T	190 +	+	160 –	↓	
8	44	T	185 +	B	130 –	↓	
9	30	T	200 +	+	(135 –)* (150 +)	↓	
10	57	T	175 –	–	140 –	↓	
11	39	T/ST	185 B	–	130 –	↓	
12	47	ST/T	190 +	–	140 –	↓	↓
13	20	T	200 –t	–	140 –	↓	
14	18	T	190 –	–	140 –	↓	
15	41	T	160 +	+	125 –	↓	
16	40	T	200 –t	–	130 –	↓	
17	29	T	190 –t	–	130 –	↓	
18	34	T	190 –t	–	130 –	↓	
19	17	T	190 –	–	125 –	↓	
20	31	T	180 +	+	130 –	↓	

Electrocardiogram: presenting abnormality, either ST segment, T wave, or both. Treadmill tests: + a positive test; – a negative test; B, borderline result; MHR, maximum heart rate; tests marked t began with T inversion which became upright during the test, returning to the original pattern during recovery. Pacing/infusion: arrows indicate direction of induced changes on T wave and ST segment.
*Negative result.

and after 80 mg oxprenolol. Because of the fast resting and maximum exercise heart rates after the beta-blocker (90 and 150, respectively), the test was repeated after 160 mg oxprenolol, when the maximum heart rate was 135 and the result negative (Table).

Those tests marked t in the Table began with inverted T waves which became upright during the test, returning to the original pattern during recovery. In the absence of ST displacement these were classed as negative.

CARDIAC CATHETERISATION

The coronary arteriogram was normal in all subjects, and there was no evidence of impaired left ventricular contraction.

PACING/INFUSION STUDIES

Both atrial pacing and adrenaline infusion influenced the ST-T segment in the same direction. Of the 16 subjects with T abnormalities, T inversion was produced or increased in all (Fig. 1 and 2), with slight associated ST depression in two.

The two subjects with ST abnormalities developed or increased ST depression (Fig. 3). Of the two with combined patterns, T inversion alone was produced in one and both ST and T changes in the other.

This synergistic effect of adrenaline on both the T wave and ST segment was striking; even when infused in doses too low to exert an effect on its own of any magnitude, it enhanced the ST-T changes produced by atrial pacing in a roughly dose-related manner (Fig. 3). Furthermore, on stopping atrial pacing the time required for ST-T changes to return to control appearances was progressively longer after the higher infusion rates. The effect of pacing invariably took several beats to reach a maximum.

Propranolol blocked the influence of adrenaline and its synergism with atrial pacing in all subjects. It did not, however, influence the effect of the atrial pacing itself (Fig. 4 and 5). Atropine (administered after propranolol) on the other hand abolished or reduced the effect of pacing in seven out of the 10 in whom it was administered (Fig. 5).

Discussion

A good correlation was apparent between the abnormality in the resting electrocardiogram and the electrocardiographic pattern induced by pacing alone or with infusion (Table). In those subjects who had originally presented with isolated T wave abnormalities or ST changes, it was usually the T wave or ST segment, respectively, that was most sensitive to manipulation by pacing/infusion.

The effects of atrial pacing and adrenaline infusion were similar and synergistic, whether they were to produce or increase T wave depression and inversion or to induce ST depression. The enhancement of the effect of pacing by adrenaline was apparent even when the dose of the latter was so low as to produce only

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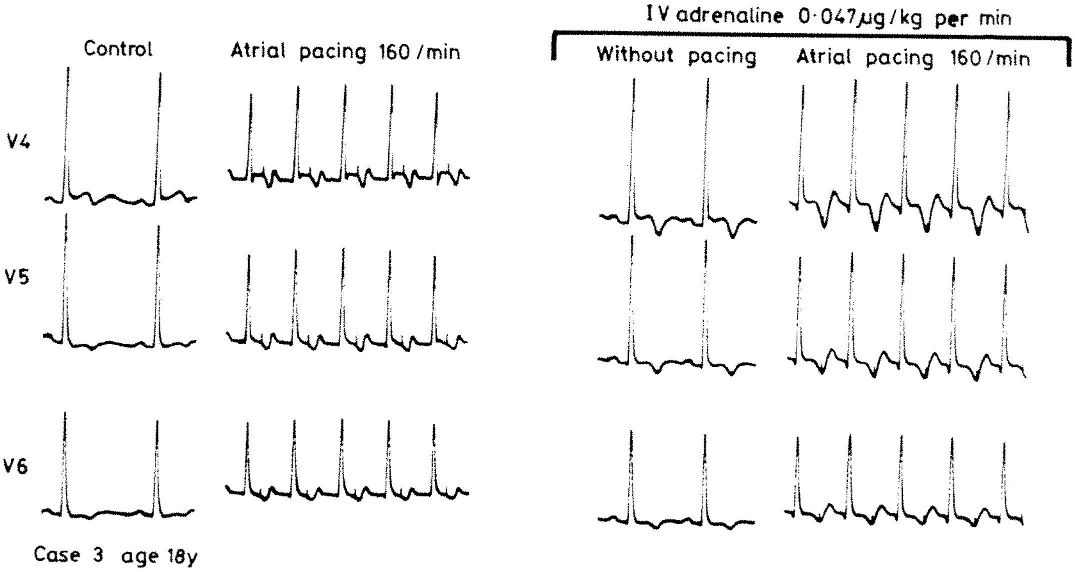

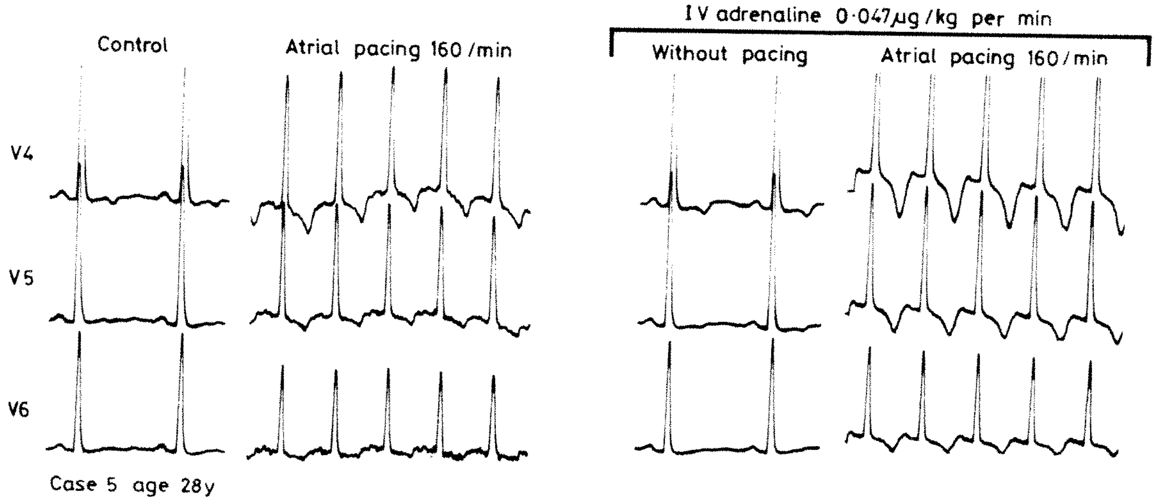

Fig. 1 and 2 *Influence of atrial pacing to 160 per min, intravenous infusion of adrenaline (0·047 µg per kg per min), and the combination of the two on the T wave of cases 3 and 5 who presented with T wave changes in their resting electrocardiogram.*

barely discernible changes on its own (Fig. 2 and 4). Pacing and adrenaline not only produce the same T wave and ST segment changes but it is also clear that they can greatly potentiate the action of each other. This potentiation might simply imply a higher non-linear relation between the overall effect (electrocardiographic changes) and the underlying mechanism (probably differential effects on action potentials in different regions of the heart). This concept is illustrated in Fig. 6. Adrenaline infusion or atrial pacing acting via the intermediary of the underlying mechanism may hypothetically exert a similar but small response on the electrocardiogram (point a). Applied together, however, and assumed to be simply additive as far as the underlying mechanism is concerned, they may produce a much larger response (point b). It is

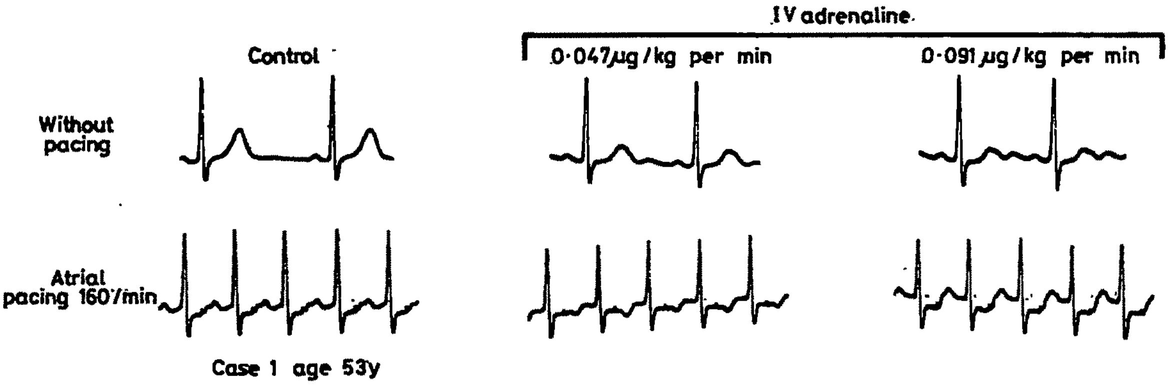

Fig. 3 *Roughly dose related ST segment depression during atrial pacing to 160 per min in response to intravenous infusion of adrenaline in two doses (0·047 and 0·091 μg per kg per min) in case 1 with intermittent ST segment changes in the resting electrocardiogram.*

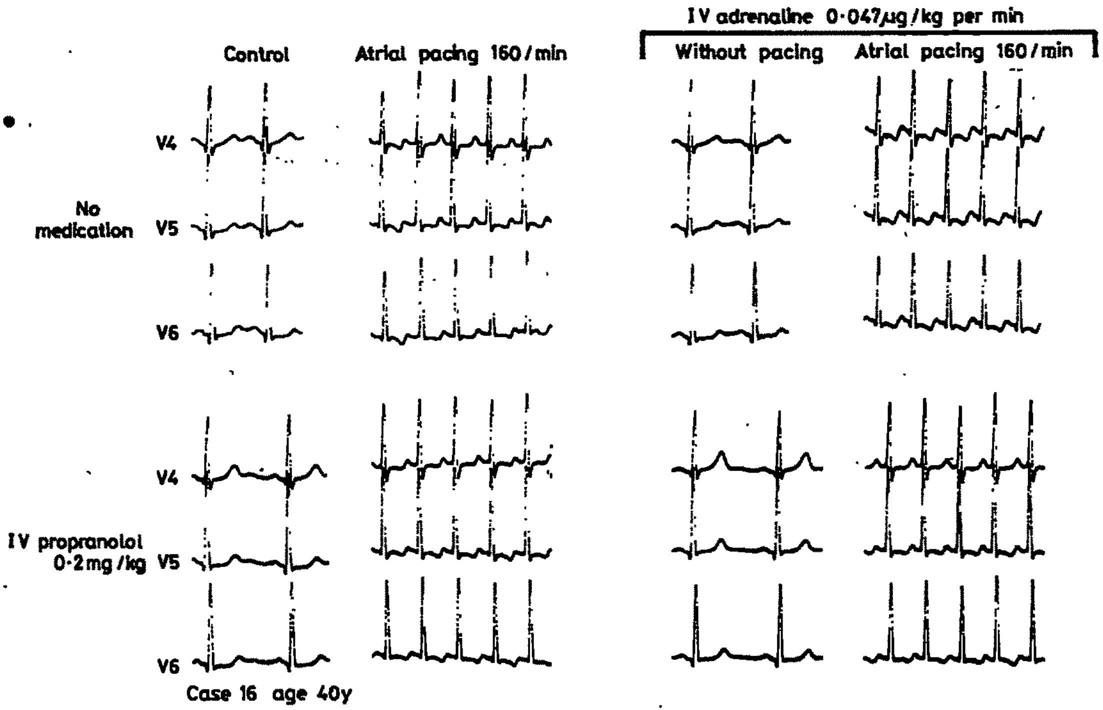

Fig. 4 *The influence of atrial pacing to 160 per min (case 16), intravenous adrenaline infusion, and the combination of the two without medication (top) and after propranolol (bottom).*

therefore not essential to assume that adrenaline directly potentiates the response to pacing to explain our results.

Control subjects were of necessity omitted from this study for obvious reasons. Lepeschkin and his colleagues,[3] however, infusing adrenaline in a dose of 0·1 μg/kg per min observed T changes in only two of 40 apparently healthy young men and even doses of 0·3 μg/kg per min induced T changes in only four of 60 young women (5·7%). ST displacement was not seen in any of their subjects. Atrial pacing per se, even when prolonged, does not influence T wave polarity in normal subjects.[4] In our experience ST or T wave changes are rare in patients undergoing routine electrophysiological studies for problems such as syncope or sinus node disease, though by no means uncom-

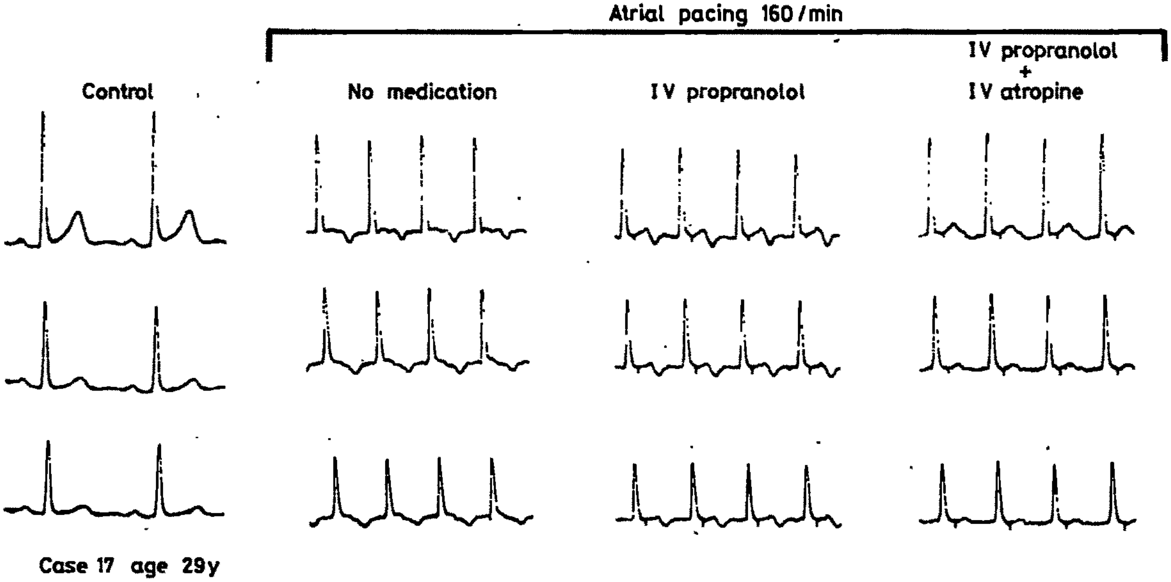

Fig. 5 *The influence of atrial pacing before and after intravenous propranolol, and after intravenous propranolol and atropine in case 17.*

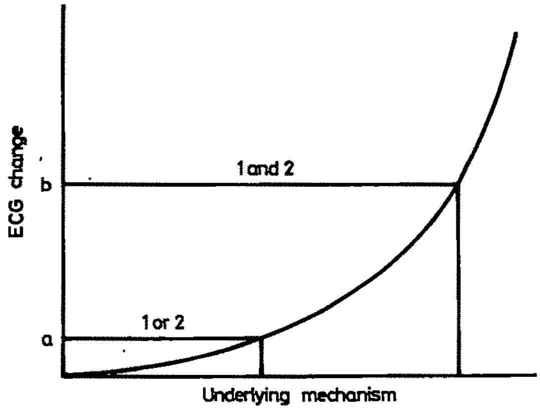

Fig. 6 *The synergism between adrenaline and atrial pacing may be explained if the effect of each on pump activity is non-linear. Adrenaline infusion (1) or atrial pacing (2).*

mon patients with angina or pre-excitation. We are unaware of any studies in which atrial pacing has been combined with adrenaline infusion; the lack of reference data and the absence of control subjects impose limitations on the interpretation of our results.

Propranolol blocked the effect of adrenaline alone and its potentiating effect on atrial pacing but did not influence the effect of the pacing itself. This suggests that when ST-T changes occur as a result of an increase in stimulation frequency they reflect a direct effect on the mechanisms responsible for the action potential duration gradients rather than an action mediated by the sympathetic. We cannot explain why atropine appeared to reduce the rate related ST-T changes induced by atrial pacing after propranolol. Acetylcholine has long been known to be without effect on the action potentials of the mammalian ventricle except in enormous concentrations,[5] probably because of an increase in potassium conductance.[6 7] Data on human ventricle, however, are lacking. It is possible that the effects of atrial pacing in these subjects were mediated via the vagus. Our observation that the effects of atrial pacing took several beats to reach a maximum would be consistent with a neurogenic reflex.

The false positive exercise test was common in those with ST segment resting electrocardiographic abnormalities, occurring in three out of four and borderline in the fourth who had mixed ST segment and T wave changes in the resting tracing. It also occurred, however, in six out of 16 (38%) subjects presenting with pure T wave abnormalities, and this is in excess of the 10% incidence expected from a random population[2] and similar to our previous findings in comparable subjects.[1]

This study is in keeping with our other observations showing that if patients with asymmetrical hypertrophy are excluded, beta-blockade will normalise a positive exercise test in those with angiographically unobstructed coronary arteries but will not influence or will only partially normalise a positive test in patients with more than 50% narrowing of at least one major vessel.[8] The mechanism of this is not clear. It is certainly not simply because of the lower maximum heart rate attained on beta-blockers, since, as shown in the Table, of the nine positive and one borderline tests without beta-blockers, five were already positive and two borderline at relatively low heart rates. Similarly, it is unlikely that the positive tests were the result of disparity between oxygen supply and demand as our subjects were asymptomatic young men without coronary artery narrowing.

While it is possible that these subjects were predisposed to coronary artery spasm, we did not feel it justified to administer ergometrine during angiography. If spasm was involved, at least some subjects should have experienced classical or Prinzmetal's angina and there should have been a higher incidence of angiographically evident obstruction.[9] Small vessel disease is also an unlikely explanation since it is usually associated with particular clinical characteristics such as systemic disease,[10] cardiac enlargement, arrhythmias, conduction disease, and syncope,[11] none of which was present in our subjects.

A more attractive explanation is that the ST depression during exercise reflects a differential effect of sympathetic activity on the plateau phase of cardiac action potentials even in normal tissue. Such explanation has been described in detail[1] and is based on action potential duration gradients thought to be responsible for creating the dipole that generates the T wave. Discussion, however, of the influence of action potential changes on the surface electrocardiogram[12] is beyond the scope of the present article.

As mentioned earlier, the normalisation of the false positive exercise test was not simply the result of the lower maximum heart rate achieved during the tests on beta-blockers, as in several instances tests were already positive early on during the subjects' previous tests at comparable heart rates, without beta-blockers. It might be inferred from the absence of any effect of beta-blockade on pacing-induced ST depression that the false positive exercise test is not purely rate dependent—if it were so false positive tests should not have been prevented by oxprenolol.

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Open aortic valvotomy for congenital aortic stenosis
Late results

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SUMMARY Forty-nine consecutive patients, aged 2 to 28 years, were followed after open aortic valvotomy. Three late deaths occurred in relation to reoperation.

Seventeen reoperations were performed 2 to 14 years after valvotomy for severe stenosis in 12 patients, aortic regurgitation in three patients, and aortic stenosis and regurgitation in two patients. Among the 12 patients who required reoperation for severe obstruction, five aged over 19 years had calcified valves with normal aortic roots and valve replacement was simple. Seven had tunnel obstruction with a hypoplastic aortic root, constituting a difficult surgical problem, and necessitating total aortic root replacement in four.

The postoperative course after simple aortic valvotomy is determined by several factors; the basic pathological form of the obstruction is the most important. Those who present in the first decade with lumpy valves and small aortic roots tend to form a diffuse tunnel obstruction when residual stenosis remains after valvotomy; older patients with pliable domed valves slowly develop calcified cusps and present less problems as the aortic root is usually a good size.

Although aortic valvotomy offers good early results with a low mortality, it should be regarded as palliative as all patients will ultimately require reoperation. Younger patients with lumpy valves and a small aortic root have more problems and may require different initial management.

Open aortic valvotomy for relief of congenital aortic valve obstruction in children and adolescents is associated with a low mortality and results are usually reported to be good or excellent.[1–6] Since the abnormal aortic valve is ultimately destined to calcify, there must be concern about the long-term future of these patients, who eventually will require aortic valve replacement.[7–9] This study was undertaken to review the fate of these patients and to see if any new or unexpected problems were encountered.

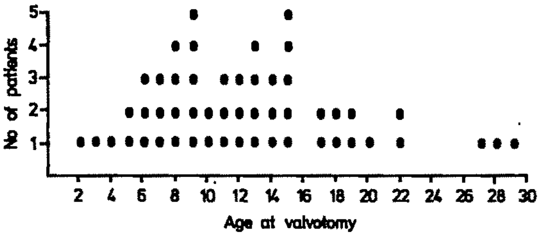

Fig. 1 *Ages of 52 patients at first open aortic valvotomy. The peak incidence occurred at 8 to 9 years and around puberty, between 12 and 15 years.*

Subjects and methods

Data on fifty-two patients with congenital aortic valve stenosis between 1961 and 1978 are presented. The age distribution of the patients at the time of operation is shown (Fig. 1)

Symptoms were present in 24 patients; dyspnoea (18), syncope (nine), angina (nine), and giddiness on effort (two). No patient had cardiac failure. Twenty eight were asymptomatic.

Two patients died and one had an immediate aortic valve replacement, leaving 49 who underwent a first open aortic valvotomy.

All patients had preoperative cardiac catheterisation but the data were available in only 48. The peak systolic pressure gradient measured across the aortic

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valve was 50 to 160 mmHg in 43 patients, exceeding 100 mmHg in 14 patients. Two patients operated on with gradients below 50 mmHg across the valve had unusual septal hypertrophy which was disproportionate to the degree of valvular stenosis; in these patients it was considered necessary to remove the valvar obstruction as a possible stimulus to excessive myocardial dysplasia.[10] The aortic valve was not crossed in three patients; the aortogram confirmed the narrow orifice of the valve and the electrocardiogram showed grade 2 left ventricular hypertrophy in one patient and grade 3 in the other two. Six patients had mild aortic regurgitation.

Table 1 *Associated congenital cardiovascular anomalies in 16 of 52 patients who had open aortic valvotomy*

Anomaly	*No.*
Coarctation	6
Persistent ductus arteriosus	4
Fixed subvalvar stenosis	3
Ventricular septal defect	1
Atrial septal defect	1
Mitral regurgitation	1
Pulmonary valve stenosis	1 (Rubella)

The associated congenital cardiovascular anomalies present in 16 patients are summarised (Table 1). Six patients had had previous surgery: three had had resection of coarctation, one had had resection of coarctation and ligation of persistent ductus arteriosus, one had had ligation of a persistent ductus arteriosus, and one a pulmonary valvotomy and ligation of a persistent ductus arteriosus.

Open aortic valvotomy was performed using cardiopulmonary bypass with normothermia or moderate hypothermia. Myocardial protection with infusion of Ringers potassium solution has been used in the National Heart Hospital since 1978. After opening the ascending aorta to expose the abnormal aortic valve, the valvotomy consisted of opening the two lateral commissures but never the anterior fused raphe. Often, despite high gradients, there was little the surgeon could do to open the valve without increasing aortic regurgitation, particularly with true bicuspid valves. In 15 patients a subvalvar myotomy was also performed because of severe subvalvar septal hypertrophy. Two patients died in the perioperative period, one of whom had a thick lumpy valve and a small aortic root, and one patient required an aortic valve replacement during the immediate postoperative period. The other 49 patients who left hospital have been followed up for two to 18 years. No patient has been lost to follow-up. All had clinical, electrocardiographic, and radiological assessment. Thirty-seven had repeat cardiac catheterisation, aortography, and left ventricular angiography.

Results

ANATOMICAL FINDINGS

In 42 patients the valve was described as "bicuspid". On reviewing the operative findings, the valve was truly bicuspid with two symmetrical or asymmetrical cusps in only 16 patients. In the other 26 the anterior cusp with the two coronary ostia was slightly larger than the posterior one and contained a rudimentary central raphe which was never opened. Truly tricuspid aortic valves were found in seven patients; in the other three patients, aged 3, 9, and 19 years, it was

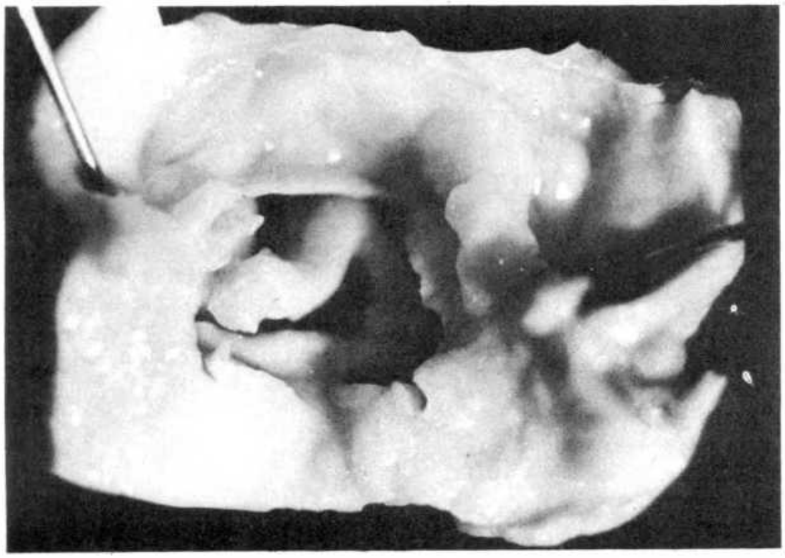

Fig. 2 *Lumpy aortic valve removed. Previous valvotomy aged 3 years. The thickened tricuspid valve is obvious.*

not possible to recognise the commissures.

Slight calcification of the valve was found in five patients, all of whom were older than 18 years.

In 14 patients the valve was thick and lumpy with nodular excrescences, sometimes resembling the cartilage of the ears (Fig. 2); 11 of these valves were bicuspid. The age of these 14 patients varied from 3 to 28 years (mean 10 years). In the other 38 patients the valves were thin and pliable.

Varying degrees of aortic root dilatation were present in all but 12 of the patients where the ascending aorta was narrow and small, as shown by angiography and confirmed at surgery. A supravalvar waist was present in the hypoplastic aortic root in six of these 12. Six of the patients with thick lumpy valves also presented with a narrow aortic root.

In 15 patients in whom myotomy and wedge resection were carried out the left ventricle was extremely hypertrophied particularly in the area of the septum. In five the angiographic findings suggested an unusually thick septum and irregular muscular thickening resembling appearances characteristic of hypertrophic cardiomyopathy. There were no correlations between the degree of hypertrophy of the left ventricle, the gradient found at cardiac catheterisation, and/or the anatomy of the aortic valve or the outflow tract.

REOPERATION

Seventeen of the 49 patients (34·7%) had a second operation on the aortic valve two to 14 years after the aortic valvotomy (Fig. 3); three patients died at reoperation. The principal indication for reoperation was severe obstruction (12), aortic regurgitation (three), or a combination of both lesions in two (Table 2). The peak systolic gradient was measured before reoperation in 14 patients and ranged from 30 to 125 mmHg (mean 79 mmHg). In most patients the resting gradient before reoperation was not as high as before the first operation (Fig. 4). The electrocardiogram became worse in seven patients and remained unchanged in the other 10. Five of the 12 patients with severe aortic stenosis had severe calcification of the valve, one of whom died after reoperation. These were the oldest patients.

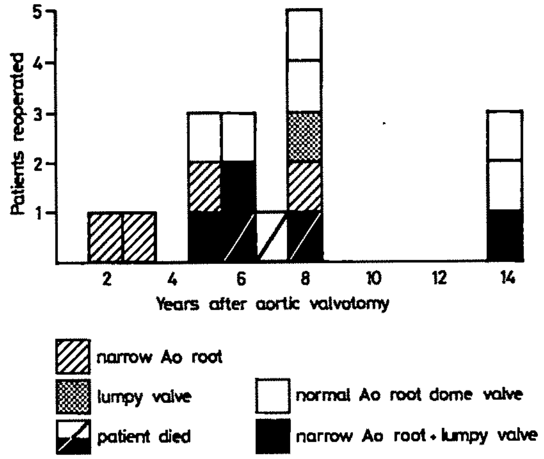

Fig. 3 *Years after aortic valvotomy in which reoperation was done, correlated with the anatomical situation of the valve and the aortic root. Patients with a small aortic root required reoperation earlier than the patients with a normal root. Two of the three deaths at reoperation occurred in patients with a small aortic root and a rigid, lumpy valve.*

Seven patients had a long "tunnel" obstruction with a hypoplastic aortic root and ring. Six had thick, lumpy valves, with nodular excrescences in three. Supravalvular waisting and subvalvular muscular hypertrophy were present in all, thus constituting a diffuse obstruction of the whole left ventricular outflow tract (Fig. 5). To relieve this diffuse obstruction four patients had total aortic valve and root replacement with a fresh, antibiotic sterilised aortic homograft with reimplantation of the coronary arteries,[11, 12] two had their valve replaced with enlargement of the aortic root with a Dacron patch; one of these patients required further operation seven years later and died during this. The seventh patient had excision of a fibrous stricture from beneath the valve which had been removed two years earlier at the time of aortic valvotomy. The valve at this time was found to be competent and not stenotic and the aortic root that had been enlarged at the time of valvotomy with a Dacron patch was found to be normal.

Three patients who had dominant aortic regurgitation had a second operation five to eight years after valvotomy. One patient, with a hypoplastic aortic root, developed severe aortic regurgitation six years after valvotomy because of detachment of one of the lumpy cusps of a bicuspid valve; he died at reoperation. In the other two, mild aortic regurgitation had been present since the valvotomy but did not become important until two and five years respectively after the first operation. At that time the valve was found to be rigid and lumpy with excrescences of cartilagenous substance in one patient and thick in the other.

Two patients presented with aortic stenosis and regurgitation requiring reoperation six and eight years after valvotomy. Both had had thick, lumpy valves with nodular excrescences which were excised. At first, aortic regurgitation was mild but it progressed suddenly after five to seven years and both were found to have holes in the left coronary cusp which had developed where the excrescences had been excised leaving holes which had been repaired with prolene sutures. One had aortic root replacement for a small aortic root and the other had an aortic homograft valve replacement which required removal four years

Table 2 *Summary of data on patients requiring reoperation, valve used for replacement, and subsequent outcome*

Age at 1st opn	*Age at reopn*	*Indication reopn*	*Findings at 2nd opn*	*Type of opn*	*Valve used for replacement*	*Outcome*
17	23	AS	Calcific aortic valve	AVR+myotomy	Pulmonary autograft	Well
19	25	AR	Lumpy aortic valve+ small aortic root	AVR+myotomy +enlarged aortic root	Pulmonary autograft	Died at 3rd operation
11	16	AR	Thick fibrotic aortic valve	AVR	Homograft	Well
6	14	AS	Thick aortic valve + small aortic root	AVR + root replacement + myotomy	Homograft aortic root + valve	Well
28	35	AS	Calcific aortic valve	AVR	Homograft	Died
15	21	AS+AR	Lumpy aortic valve + hole cusp + small aortic root	AVR + root replacement	Homograft aortic root + valve	Well
12	17	AS	Thick aortic valve + small aortic root	AVR + myotomy + enlarged aortic root	Starr	11 y later mitral + ao valve repl.
6	14	AS+AR	Lumpy aortic valve + hole cusp	AVR	Homograft	4 y later ao root + valve repl.
27	35	AS	Calcific aortic valve	AVR	Homograft	Well
8	22	AS	Lumpy aortic valve + small aortic root	AVR + root replacement	Homograft aortic root + valve	Well
13	15	AS	Aortic valve thin, competent, + subaortic ring, + small aortic root	Relief of subaortic obstruction		Well
7	15	AR	Lumpy aortic valve, + detachment of cusp, + small aortic root	AVR + myotomy	Homograft	Died
3	8	AS	Lumpy aortic valve, + small aortic root	AVR + root replacement	Homograft aortic root + valve	Well
9	23	AS	Calcific aortic valve	AVR + myotomy	Homograft	Well
5	8	AS	Thick aortic valve, + small aortic root	AVR + root replacement + myotomy	Homograft aortic root + valve, + pacemaker	Well
9	17	AS	Thick, lumpy aortic valve	AVR	Homograft	Well
15	29	AS	Calcific aortic valve	AVR	Homograft	2 y later AVR

AVR, aortic valve replacement; opn, operation; AS aortic stenosis; AR, aortic regurgitation.

later because of calcification.

No patient had a history or any signs of infective endocarditis at reoperation.

One 10-year-old boy required mitral valve surgery five months after aortic valvotomy for iatrogenic mitral regurgitation. This was a patient with severe subvalvar hypertrophy who had had a deep myotomy and wedge resection of myocardium which had disturbed the submitral valvar mechanism leading to ruptured chordae with a flail anterior cusp.

STATE OF SURVIVORS

Thirty-two patients have not yet had a second operation during the two to 18 years of surveillance (mean 6·3 years). Twenty have had cardiac catheterisation during the follow-up period and two patients had catheterisation repeated five and seven years after the first study.

Fifteen patients had moderate residual lesions with a gradient of 30 to 70 mmHg (Table 3); only three of these patients have symptoms. In seven patients with

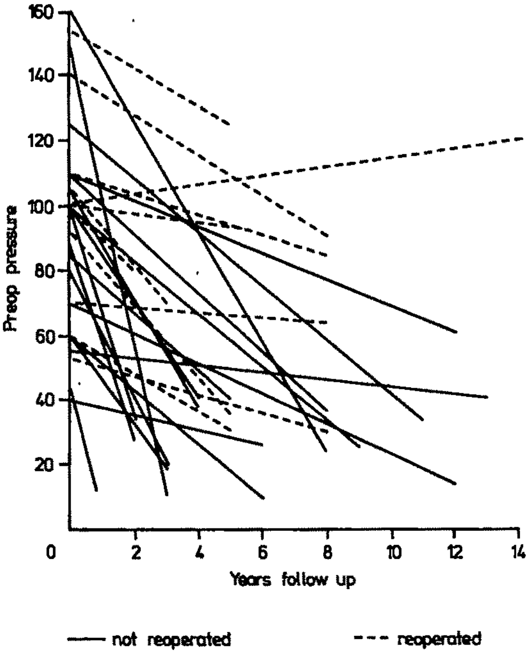

Fig. 4 *Peak systolic gradients in patients with congenital valvular aortic stenosis, recorded preoperatively and at postoperative catheterisation done at different years of follow-up. In the first few years after the operation there is a pronounced fall in the peak systolic gradient, but it tends over the years to approach the preoperative level again.*

predominant stenosis, signs of obstruction were still present immediately after the valvotomy but they have remained relatively stable during the following years. The two who both had repeated catheterisation at 5 and 7 years after their first study did not show any changes in gradient. Two patients with progressive obstruction had thick lumpy valves and a small aortic root. Among the patients with moderate aortic regurgitation, a mild early diastolic murmur was heard immediately after the operation in only five. No patient has had bacterial endocarditis during the period of observation. No correlation was found between the presence and the degree of aortic regurgitation and the anatomical condition of the valve (bicuspid or tricuspid, lumpy or pliable) and/or the characteristics of the aortic root.

Thirteen asymptomatic patients had aortic valve stenosis with a resting gradient below 30 mmHg and/or trivial aortic regurgitation, static for one to 11 years. Three of these had lumpy valves and a small aortic root, factors that seem to predispose to the development of "tunnel" obstruction when residual obstruction is left behind; the aortic root had been enlarged with a pericardial patch at the time of valvotomy in all these.

Four of the 49 patients had excellent results and three to four years after valvotomy retained only a short soft systolic murmur with a late click and a normal electrocardiogram. Severe calcification of the aortic valve developed gradually in five patients above the age of 19 years followed for six to 18 years, with moderate stenosis.

Twelve patients who presented at the time of the first operation with extreme left ventricular hypertrophy on angiography were also given isoprelaline at postoperative cardiac catheterisation; in nine (Fig. 6) the subvalvar gradient was trebled. It was decided to give propanolol to four of these patients in the hope of preventing further hypertrophy and subvalvar obstruction as the electrocardiogram continued to show grade 3 changes and angiography showed severe and irregular muscular hypertrophy.

Fig. 7 shows the actuarial curve of survival following aortic valvotomy. After 18 years of follow-up 80% of patients were alive, with 98% survival in the first seven years. The proportion of patients alive with their own aortic valve (without reoperation) at 20 years, however, was only 14%, which means that if the standard error of 12% is taken into account, all patients will require reoperation within 20 years of follow-up.

Discussion

This group of patients is typical of congenital aortic valve stenosis which presents in childhood and adolescence. It excludes infants who present with critical aortic valve stenosis, however, whose problems are different since there is so much infarction (necrosis) in the left ventricle and the cusps are always poorly formed.

In most of the series of congenital aortic valve stenosis that we have reviewed[13-19] there is no mention of the unusual form of the thick lumpy valve with a small aortic root. Some authors[3] describe "some thick valves with thickening of the cusps particularly along the leading edges". Other authors[6] describe multiple levels of stenosis. In 1971 Somerville and Ross[20] pointed out an unusual form of congenital aortic stenosis which may be part of a more diffuse abnormality. Fisher *et al*[5] described three out of 45 patients with various forms of congenital aortic stenosis who presented with "a tunnel aortic stenosis, characterized by hypoplasia of the aortic valve ring and ventricular outflow tract, by thickened valve leaflet and by underdeveloped ascending aorta". They pointed out that this posed a difficult technical problem to relieve.

In the present series it is clear that the late mortality is related to reoperation, as in other series.[17] A cause for concern is that the operative mortality for the first

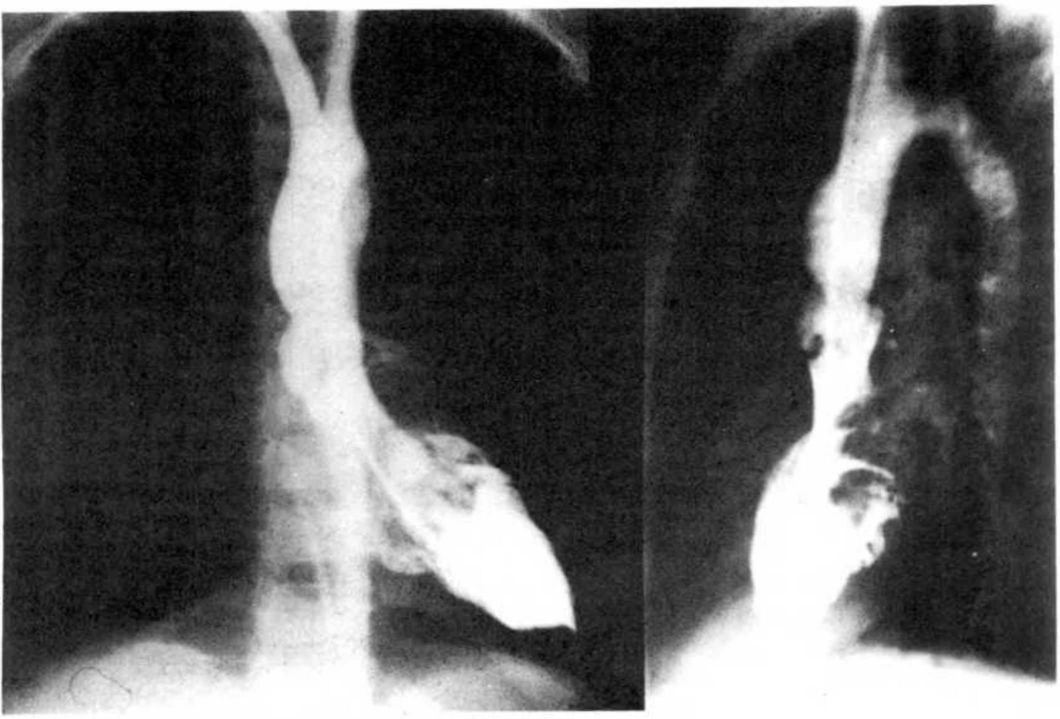

Fig. 5 *Left ventricular angiograms from a patient with a tunnel obstruction who needed aortic valve and root replacement: small aorta with supravalvular waist, thick distorted aortic valve, and extreme hypertrophy of muscle in the left ventricle are present. The patient aged 13 years had the first aortic valvotomy at the age of 3 years.*

Table 3 *State of 32 patients who have had open aortic valvotomy and have not yet required reoperation*

	No.	*Calcified aortic valve*	*Lumpy valve + small aortic root*	*Static since operation (follow-up years)*		*Progressive (follow-up years)*		*Electrocardiogram*		
								Improved	*Unchanged*	*Deteriorated*
Moderate aortic stenosis gradient 30–70	5	3	2	3	(4–13)	2	(2–11)		3	2
Aortic stenosis aortic regurgitation	10	2		4	(5–8)	6	(6–18)	4	5	1
Mild aortic stenosis gradient <30	13		3	13	(1–11)			7	5	1
Excellent	4			4	(3–4)			4		
Total	32	5	5	24		8		15	13	4

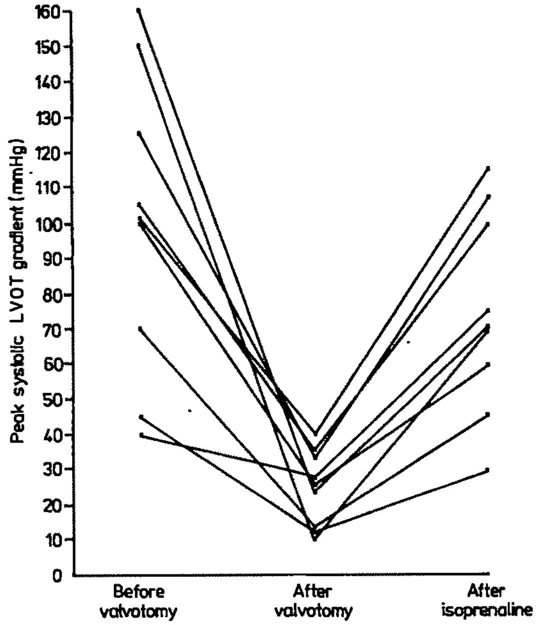

Fig. 6 *Peak systolic gradients across the left ventricular outflow tract preoperatively, and postoperatively at rest and after isoprenaline stimulation in nine patients, all of whom had extreme left ventricular hypertrophy on angiography preoperatively. Isoprenaline produced a distinct increase in the gradient in all nine patients.*

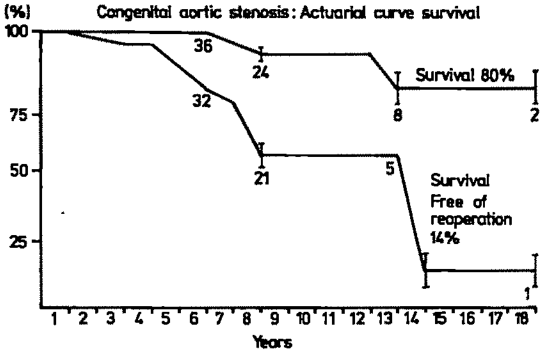

Fig. 7 *Actuarial survival curves of 49 patients who had open aortic valvotomy: survival at 18 years of follow-up, upper curve reoperation; lower curve no reoperation. Bars show ± standard error at various points.*

reoperation in this group of relatively young patients is considerably higher (17%) than for a routine first aortic valve replacement (6%) and for a first aortic valvotomy (4%).

The problem of progressive aortic regurgitation was small in this group, though other reports suggest it is the most common cause for reoperation being needed.[15] [16] Perhaps the careful techniques used here prevented important regurgitation but left more obstruction. Where myxomatous masses of nodular excrescences had been excised, the cusps appeared to weaken and later rupture, causing an acute increase in aortic regurgitation. Thus, this procedure should not be undertaken lightly even though it is simple. Patients with the small roots and lumpy valves when left with aortic regurgitation were easier to manage at reoperation as tunnel obstruction did not form.

Infective endocarditis was not responsible for any deterioration in valve function in this group. Gersony and Hayes[21] have suggested that aortic valvotomy may increase the risks of infection but since endocarditis is age-related one might expect an increase anyway in the "ageing" postoperative patients. There have been none seen yet in our patients, however, and we doubt if surgery increases the risk of this complication.

Excluding the few problems with aortic regurgitation and the occasional production of mitral regurgitation it appears that there are two courses which patients may take after the first aortic valvotomy. One, slow degenerative calcification, which is relatively simple to manage, and the other with hypoplasia and tunnel obstruction which is difficult and dangerous. The determinant of what happens after aortic valvotomy is the pathological anatomy of the valve at the first operation. Patients at risk of having a difficult reoperation are those with the less common form of congenital aortic valve stenosis described as an atypical variant by Somerville and Ross.[20] In our experience this form occurred in 24% of patients; the ring, root, and ascending aorta are small and there is often abnormal subvalvar septal muscle which can form a long obstruction if distal stenosis in the root or valve persists. This type of obstruction resembles the form which occurs in infancy and perhaps represents the milder variety of the same pathology. We think this form is really part of diffuse congenital cardiovascular disease, differing from the more simple and common form of congenital aortic valve stenosis, the pliable dome, which is usually associated with a normal root and post-stenotic aortic dilatation and more often presents later in adolescence.

The type of aortic valve stenosis must be recognised before the first operation, as the operative procedure required may need modification and the ultimate prognosis is different. It is important that those with lumpy valves and hypoplasia of the aorta have good and near complete relief of obstruction; in those below 7 to 8 years we would prefer not to replace the whole root and would therefore recommend gusseting it and leaving some aortic regurgitation to open the outflow. In the few older patients over the age of 10 years who present for the first operation with this form of aortic valve stenosis, aortic root and valve replacement would now be advised as we feel this procedure provides better long-term relief of the obstruction and is better for the long life of the left ventricle. Unfortunately, these lumpy dysplastic valves are more common in those who present with critical aortic valve stenosis in the first decade. The first operation, which may be regarded as simple, determines the patient's fate which may be unexpectedly disastrous at reoperation.

Another factor that can contribute to subsequent surgical problems is the unusual disproportionate septal hypertrophy present in some patients, particularly in those with small aortic roots. In our series all these patients had myotomy at the time of valvotomy but we cannot show that myotomy is beneficial as those with and without it are not comparable groups. We think, however, that much more important than performing a myotomy is to leave behind only trivial fixed obstruction. Seventeen patients (35%) have already required reoperation and another one has obvious radiological calcification. Some valve calcification, suggested by the echocardiogram, may be present in a further nine but is not obvious radiologically. The rate of reoperation in patients with calcification is reported in a few series[14 16] and seems to be related to the length of follow-up. More time must elapse before the complete story is known, but we predict that all will have required reoperation before the end of the second decade. What is needed is something to prevent valve calcification. Restenosis of the aortic valve probably does not occur in the way it does after mitral valvotomy. Obstruction becomes critical from increased rigidity, non-growth of the area, or effects of residual obstruction left at the first operation; this occurred in two patients whose gradients were 80 and 60 respectively after valvotomy and who will require reoperation earlier than the rest. Eight patients who did not need reoperation were followed for more than 10 years and the stenosis had been midly progressive in four of them. Five of these patients are women who may fare better.

Many reports have claimed good or excellent results for open aortic valvotomy. We accept this if judged by the patient's early survival, early well-being, and improvement in variables which reflect left ventricular performance. Long-term survival without major problems, however, is now of more concern. At best, open aortic valvotomy can be considered to offer only good palliation, reoperation associated with many problems and some risks being inevitable in the future. The diseased damaged aortic valve remains in the patient and, after valvotomy, the most that can be offered is replacement by a valve with limited life span, known and unknown complications, and inevitable rereplacement. We believe that it is better for a patient to retain, as long as possible, his own aortic valve provided there is no damage occurring to the left ventricular myocardium nor the development of secondary changes which may prejudge the results of reoperation. Thus, aortic valvotomy has an important place in the management of critical aortic valve stenosis, but it is just as important not to do it too early as it is not to do it too late after irreversible myocardial damage.

A knowledge and understanding of the valve pathology before valvotomy may allow more correct prognosis and improve management.

It is also mandatory to establish in the first postoperative year the extent of the residual lesion, keep the patient under regular supervision, and discourage the pursuit of activities which overload the already damaged or "at risk" left ventricular muscle. At the time of the first valvotomy, the future must be seriously considered, knowing that at some time a surgeon must operate again. The goal of aortic valvotomy should be to relieve as completely as possible the obstruction without producing serious aortic regurgitation, and thus improve the life and function of the left ventricle.

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Addendum

Since submitting this paper for publication in 1980, two more patients have had either valve replacement or valve and root replacement, seven and 15 years after the first valvotomy. One developed progressive calcification and the other with a lumpy valve had a tunnel obstruction.

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Atresia of left atrioventricular connection
Surgical considerations

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SUMMARY We have studied 17 patients diagnosed in life as having absent left atrioventricular connection (14 patients) or an imperforate left atrioventricular valve (three patients). Ten patients presented below the age of 3 months with tachypnoea, mild cyanosis, and heart failure. Seven patients, including two with moderate and one with severe pulmonary outflow tract obstruction, presented at a mean age of 45 months (range six months to 16 years). Six patients had a non-restrictive interatrial communication when first catheterised. In the remainder the mean interatrial gradient was 14 mmHg. Excluding patients with pulmonary outflow tract obstruction the mean pulmonary vascular resistance was 6·7 units/m^2. Patients were managed by balloon atrial septostomy (four patients), atrial septectomy (nine patients), pulmonary artery banding (nine patients), systemic-pulmonary anastomoses (one patient), and a modified Fontan's procedure (one patient). There were five hospital deaths. Two followed pulmonary artery banding and three followed atrial septectomy. The mean length of follow-up in the surviving patients is 5½ years (range five months to 15 years). The six patients who had an atrial septectomy, and one patient who had a modified Fontan's procedure, are well palliated with minimal reduction in exercise tolerance and mild cyanosis at rest. Three patients, one with an atrial septostomy, one who had pulmonary artery banding, and one who had no surgical procedure have evidence of pulmonary vascular disease. A further patient who had a balloon septostomy has electrocardiographic evidence of left atrial hypertrophy. We conclude that atrial septectomy plus or minus pulmonary artery banding provides good palliation and prevents the development of pulmonary vascular disease. A modified Fontan's procedure should be considered as an alternative or subsequent procedure in patients with suitable anatomy.

Atresia of the left atrioventricular orifice in atrial situs solitus is a rare congenital heart defect.[1–3] The majority of cases also have aortic atresia with a correspondingly poor prognosis. Those cases which have a patent aortic root have a better prognosis,[4 5] the longest survival without palliation being in those with an associated non-restrictive interatrial communication and mild to moderate pulmonary stenosis.[6] In this report we describe our experience with the surgical management of patients with absent left atrioventricular connection or imperforate left atrioventricular valve in situs solitus, a topic recently discussed elsewhere.[7] We used palliative procedures designed to relieve left atrial hypertension and to render pulmonary blood flow optimal. In addition we were able to perform a successful modified Fontan's procedure in one case.

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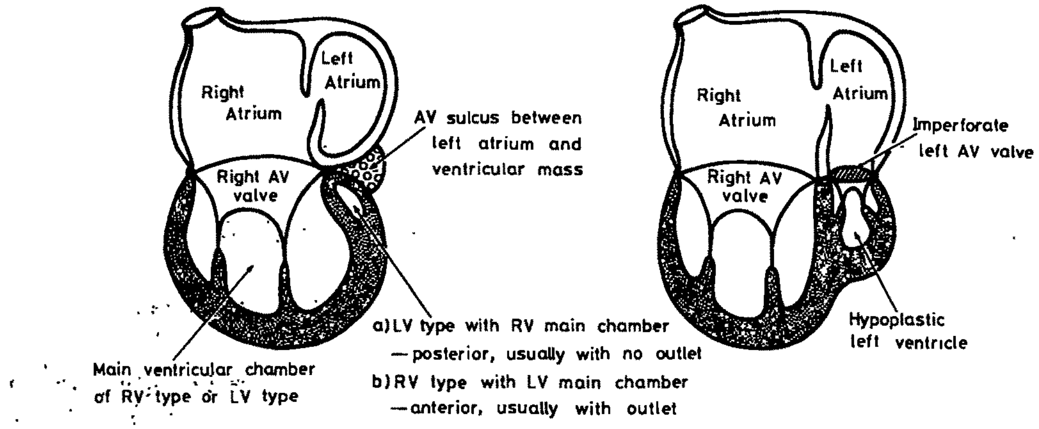
Patients

Fourteen patients with absence of the left atrioventricular connection and three patients with an imperforate left atrioventricular valve with patent subaortic outflow tract were seen at the Brompton Hospital between January 1964 and June 1980. Absent left connection is diagnosed when there is no communication, either actual or potential, between the floor of the left atrium and the underlying ventricular mass. The atrial floor is completely separated from the ventricle by atrioventricular sulcus tissue (Fig. 1a). We separated these hearts from those in which an imperforate membrane was interposed between the left atrium and the ventricular mass, these two structures therefore being potentially connected (Fig. 1b). The presence or absence of a valve membrane with accompanying hypoplastic subvalvar


Right Atrium
Left Atrium
Right AV valve
AV sulcus between left atrium and ventricular mass
a) LV type with RV main chamber —posterior, usually with no outlet
b) RV type with LV main chamber —anterior, usually with outlet
Main ventricular chamber of RV type or LV type
Right Atrium
Left Atrium
Imperforate left AV valve
Right AV valve
Hypoplastic left ventricle

(a) Absent left atrioventricular connection (b) Imperforate left atrioventricular valve

Fig. 1 *(a) Absent left atrioventricular connection. Note atrial floor is completely separate from the ventricle by atrioventricular sulcus tissue. (b) Imperforate left atrioventricular valve in which the left atrial and ventricular cavities are potentially connected.*

apparatus has been subsequently confirmed in all surviving patients by echocardiography.

CLINICAL PRESENTATION

Ten of the 17 patients presented in the first three months of life. Nine of these had tachypnoea, mild cynosis, and congestive cardiac failure, and the tenth had moderate cyanosis. Seven patients presented between the age of 6 months and 16 years. Symptoms in this later group consisted of either increasing cyanosis, decreasing exercise tolerance, or failure to thrive.

CARDIAC CATHETERISATION

Five patients had serial cardiac catheterisations and the total number of cardiac catheterisations performed was 26. Data from these are presented in Table 1. Six patients had an interatrial gradient of less than 5 mmHg at the time of their first catheterisation. Excluding those with a non-restrictive atrial septal defect, two of the patients who had an interatrial gradient of less than 5 mmHg at the time of their first catheterisation have been recatheterised, three and seven years later. In one the interatrial gradient had risen to 13 mmHg and in the other it was not possible to enter the left atrium. Two patients had evidence of moderate and one patient of severe pulmonary outflow tract obstruction. The mean pulmonary vascular resistance, excluding those patients with pulmonary outflow tract obstruction, was 6·7 units/m^2. One patient had evidence of subaortic obstruction.

ANGIOGRAPHY

Selective left atrial injections were performed in all but two patients and confirmed that there was no direct communication between the left atrium and the ventricular mass. The left atrium was visualised on the follow-through in one of the remaining patients and in the other the diagnosis was confirmed at operation.

In the cases with absent left atrioventricular connection, the right atrium was connected via the right atrioventricular valve to a left ventricular chamber in seven patients, a right ventricular chamber in four patients, and a single chamber of indeterminate morphology in three patients. All patients with main chambers of left ventricular type also possessed anterior rudimentary chambers of right ventricular type. In one of these the rudimentary chamber was right sided and supported the pulmonary trunk. In the remaining six the right ventricular chamber was either directly anterior or left sided and supported the aorta.

Rudimentary chambers of left ventricular morphology were present in all four patients with main ventricular chambers of right ventricular type. In all the left ventricular chamber was left sided and posterior, being simply a trabecular pouch with neither inlet nor outlet portions, both great arteries arising from the right ventricle. In these four the aorta was posterior and to the right in two, and anterior and to the right in the other two. This was in contrast to the three patients with atrioventricular concordance and imperforate left valve membranes. In these three

Table 1 *Catheter data*

Case No.	*Age*	*PAP*	*AOP*	*QP*	*LAP*	*RAP*	*% O_2 SAT*	*PVR*
1	4 wk	77	—	3·5	25	4	70	8·8
2	2 y	96	90	—	—	3	70	—
3	1 y	45	100	5·9	11	11	74	0·8
	8 y	28	90	1·7	20	7	88	4·1
4*	19 mth	80	80	7·0	11	3	75	6·1
5	16 y	—	125	—	5	3	76	—
6	6 wk	—	100	—	19	19	—	—
	3 y	—	80	3·6	5	5	78	—
	6 y	—	100	—	19	19	79	—
	10 y	—	90	4·6	9	9	86	—
7*	8 mth	85	83	2·4	9	5	84	8·4
8*	2 mth	84	76	2·4	—	11	65	—
9†	6 wk	59	70	5·6	9	4	74	5·3
	5 mth	80	62	3·4	17	12	68	12·0
10	3 wk	40	65	2·1‡	11	4	88	6·5
11	6 wk	76	76	2·6	27	3	64	8·0
12	3 wk	—	75	5·2	21	9	70	—
13	4 wk	—	—	1·1	25	3	—	—
14	5 y	85	90	9·1	18§	5	91	5·7
15	5 wk	80	85	5·2	—	9	94	6·2
	7 wk	35	60	5·4	20	40	81	1·3
	6 y	25	100	3·6	11	11	80	—
	10 y	47	75	2·5	7	5	77	—
16●	6 mth	66	75	—	16	12	84	—
	3 y	68	87	3·2	—	2	76	12·0
17	3 mth	55	—	5·1	4	4	—	5·4

* Postoperative death. † Operative death. § Pulmonary artery wedge. ‡ Effective pulmonary flow.
PAP, pulmonary artery pressure; AOP, aortic pressure; QP, pulmonary flow; LAP, left atrial pressure; RAP, right atrial pressure; PVR, pulmonary vascular resistance.

patients the hypoplastic left ventricle gave rise to the aorta, the ventricles and great arteries being normally related.

In the three remaining patients with absent left atrioventricular connection, the right atrium was connected with a single ventricular chamber of indeterminate type, both great arteries arising from this ventricle. The aorta was directly anterior in one patients, in the left posterior position in one patient, and in the right posterior position in the remaining case.

Associated anomalies in the group as a whole included persistent ductus arteriosus in one case, juxtaductal coarctation in two cases, partial anomalous venous drainage with the right pulmonary veins entering the superior vena cava in two cases, left superior vena cava in four cases, and stenosis of the superior vena cava in one case.

Balloon atrial septostomy was performed in four patients at the end of cardiac catheterisation.

SURGERY

The operations in the sequence in which they were performed are outlined in Table 2.

Atrial septectomy was performed in nine patients. In those patients presenting in the first three months of life, atrial septectomy was performed by inflow

Table 2 *Surgical precedures performed in each patient*

Case No.	*Age*	*Procedure(s)*
1	4 wk	Septectomy, PA banding
2	2 y	Septectomy, PA banding, relief of SVC obstruction
3	8 y 7 mth	Septectomy, pulmonary valvotomy
4*	5 y	Septectomy
5	16 y	Modified Fontan's
6	5 y	Waterston
	5 y 4 mth	Potts
7*	9 mth	PA banding
8	3 mth	Septectomy
9	4 wk	Resection coarctation division, PDA ligation, PA banding
	2 mth	Septectomy
10†	2 mth	Resection coarctation
	5 mth	PA banding
	5¼ mth	Septectomy
11	3 wk	Septostomy
	4 wk	PA banding
	5 wk	Septectomy
12†	6 wk	Septostomy
	6 wk	Septectomy
	8 wk	PA banding
13	3 wk	Septostomy
	6 wk	PA banding
14	4 wk	Septostomy
15	—	—
16	6 mth	PA banding
17	4 mth	PA banding

* Operative death. † Postoperative death.

occlusion. In older patients septectomy was performed using cardiopulmonary bypass. This is our preferred method in these patients because a complete septectomy can be performed and it allows detailed inspection of the intracardiac anatomy. Banding of the pulmonary artery was performed in ten patients, resection of a juxtaductal coarctation was performed in two patients, and ligation of a persistent ductus arteriosus in one. One patient had a complete stenosis of the superior vena cava and partial anomalous venous drainage, and a Goretex graft was inserted between the superior vena cava and the right atrium at the time of atrial septectomy.

A more physiologically corrective procedure was performed in one girl. She presented at the age of 16 years with increasing cyanosis, dyspnoea on exertion, and a past history of two cerebrovascular accidents. Cardiac catheterisation and angiography disclosed absent left atrioventricular connection in association with a univentricular heart of left atrioventricular type with concordant ventriculoarterial connections and normally related great arteries (Holmes heart with mitral atresia).[8] At operation she was found to have a large secundum atrial septal defect. An interatrial baffle was constructed to divert the pulmonary venous blood through the right atrioventricular valve. An aortic homograft valve was then placed at the junction of the inferior vena cava and the right atrium. The rudimentary right ventricular chamber was opened, the outlet foramen closed, and a 1·8 cm preclotted woven Dacron tube placed between the right atrial appendage and the outlet chamber (Fig. 2).

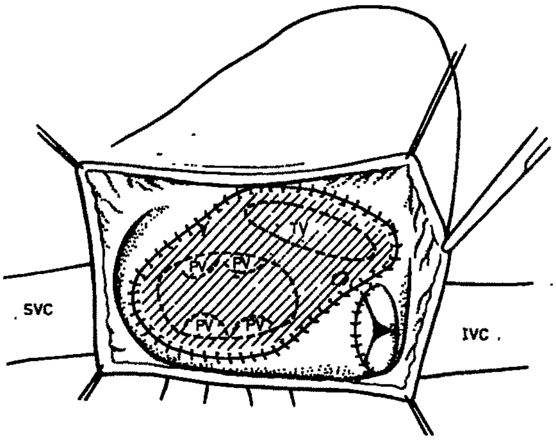


Fig. 2 *An intra-atrial baffle has been placed to direct blood from the four pulmonary veins (PV) into the orifice of the right atrioventricular valve (TV). Systemic venous return from the superior vena cava (SVC) and inferior vena cava (IVC) is directed into the pulmonary artery by a modified Fontan's procedure, not shown in the drawing.*

HOSPITAL MORTALITY

There were five hospital deaths. Three followed septectomy and two followed pulmonary artery banding. All three patients who died after atrial septectomy had evidence of raised pulmonary vascular resistance and in addition one also had evidence of subaortic obstruction. Of the two patients who died after pulmonary artery banding, one had atrioventricular valve regurgitation and the other had a cardiac arrest after accidental removal of the endotracheal tube and suffered irreversible brain damage.

FOLLOW UP

Systemic oxygen saturation was increased by septectomy in all but one patient, including those patients who had a simultaneous pulmonary artery banding (Table 3). One patient had a particularly dramatic increase in oxygen saturation from 64 to 95%. Pulmonary artery banding was subsequently required and in retrospect should have been performed at the time of septectomy. Of the six patients who have had a septectomy, five have also had pulmonary artery banding. Follow up in these patients ranges from five to 150 months with a mean of four years. None of the patients had more than minimal reduction in exercise tolerance: two are pink at rest and the other four are minimally desaturated.

One patient underwent balloon septostomy seven years ago. He is at present well but has clinical evidence of pulmonary hypertension. In retrospect he should have had pulmonary artery banding.

Another patient who underwent balloon septostomy followed by pulmonary artery banding is well but has electrocardiographic evidence of left atrial hypertrophy.

Another patient catheterised 10 years ago at the age of 5 years had neither balloon septostomy nor pulmonary artery banding in spite of the fact that her pulmonary artery pressure was at systemic level, and there was a gradient of 13 mmHg between the right

Table 3 *Absent left atrioventricular connection*

% O_2 *Saturation*	
Before septectomy	*After septectomy*
81	77*
70	88†
80	91*
64	95‡
70	90†
88	91
75	87§
76±10%	89±6%

* Previous banding. † PA banding.
‡ Banding required 2 weeks later. § Postoperative death.

atrial and pulmonary artery wedge pressure. She now has clinical evidence of pulmonary hypertension.

A further patient who had pulmonary artery banding at the age of 6 months, did not have atrial septectomy because the interatrial gradient at this time was only 4 mmHg, and now there is clinical evidence of left atrial hypertension; when recently recatheterised the left atrium could not be entered.

The patient who underwent a modified Fontan's procedure at the age of 16 required a further operation to relieve stenosis at the distal end of the conduit produced by pseudoendothelial encroachment. She is now aged 20 and leads an active, virtually normal, life.

There have been no late deaths in this series.

Discussion

Left atrioventricular valve atresia in patients with situs solitus is most frequently associated with atresia of the aortic root.[1-3] In this situation systemic and coronary blood flow depends upon a persistent ductus arteriosus and most patients die in the first few days of life. In contrast, when atresia of the left atrioventricular valve is associated with a patent aortic root, survival beyond the neonatal period is much more frequent. If suitable palliative procedures enhance survival in this group, then more corrective surgical procedures can be envisaged during childhood.

Mickell *et al.*[6] recently reviewed their clinical experience with this group of patients, and described how palliative procedures should be designed first to optimise pulmonary blood flow and second to relieve left atrial hypertension. Our findings confirm their observation that left atrial hypertension caused by inadequate interatrial communication can be identified on serial cardiac catheterisations in the majority of patients. In both series, such hypertension was progressive but was not always associated with obvious clinical deterioration. Relief of left atrial hypertension, by balloon atrial septostomy in infancy or atrial septectomy in older patients, should therefore be provided as soon as a restrictive interatrial communication is identified. Banding of the pulmonary artery should be performed in those patients without naturally occurring pulmonary outflow tract obstruction, to prevent the development of pulmonary vascular disease. There is a significant early mortality after palliative procedures. This may well be related to the fact that pulmonary vascular disease had already developed in some cases, thus emphasising the necessity for early surgical intervention.

The need for continuous reassessment and recatheterisation, pointed out by Mickell *et al.*,[6] is well illustrated by three patients in our series. In two, non-restrictive interatrial communication became restrictive in later life while the other developed a restrictive interatrial communication after balloon septostomy.

There was too few patients in our series with pulmonary outflow tract obstruction to support the conclusion of Mickell *et al.*[6] that the prognosis was best in those with mild to moderate pulmonary stenosis. Having performed palliative surgery to provide to the best of our ability the ideal situations outlined above, all the patients in this series bar two have minimal limitation of exercise tolerance and are leading virtually normal lives. The two outstanding patients are severely restricted. One has severe pulmonary outflow tract obstruction and one has developed a restrictive interatrial communication and is awaiting surgery.

The possibilities for more "corrective" surgery are illustrated by our case managed successfully by a modified Fontan's procedure, a procedure not to the best of our knowledge previously performed for this anomaly but suggested recently by Rao *et al.*[7] Our patient is leading a normal and active life at the age of 20, four years after operation. It must be said, however, that the particular morphology in this case, though ideal for the operation, is a rare combination. There was ventriculoarterial concordance in association with a univentricular heart of left ventricular type. This permitted the rudimentary right ventricular chamber to be incorporated into the pulmonary circuit as is possible in classical tricuspid atresia.[9] More usually, as illustrated in our series and other reported cases,[10] the ventriculoarterial connection is discordant when absent left atrioventricular connection is found in association with a univentricular heart of left ventricular type. If "corrective" surgery were envisaged in these cases, it would be necessary, after rerouting of atrial blood, to connect the newly constructed right atrium directly to the pulmonary arteries. Similar procedures will probably be required when absent left atrioventricular connection is found in association with a univentricular heart of right ventricular type. In the four hearts of this type in our series both great arteries arose from the right ventricular main chamber, the rudimentary left ventricular chamber being simply a trabecular pouch of no value for incorporation within either circuit during reconstructive surgery. Similarly, in those patients with absent left connection in association with sole ventricular chambers of indeterminate type, "corrective" surgery would entail septectomy, division of the common atrial chamber thus created, and connection of a newly created right atrium directly to the pulmonary arteries. The success of such operations may therefore be limited, since propulsion of the pulmonary circulation will depend on a newly created systemic venous atrium with less than its normal musculature. Only experience will show whether such a modified Fontan procedure is possible. What can be stated is that for such an operation to have any chance of success, the pulmonary vascular resistance must be low.[11] This re-emphasises importance of early palliative procedures to relieve left atrial hypertension and to curtail excessive pulmonary blood flow.

It is also highly likely that a modified Fontan procedure would be the most suitable "corrective" procedure in those cases which have imperforate left atrioventricular valves in association with atrioventricular concordance. In such hearts in our series, though the left atrium was connected to the hypoplastic left ventricle, the valve membranes and their tension apparatus were grossly hypoplasitc. It did not seem feasible to insert a prosthetic valve in this small left atrioventricular orifice even if it proved possible to remove the imperforate valve membrane. Equally, the left ventricle itself seemed so hypoplastic as to be incapable of supporting the circulation if septation had been attempted in combination with re-establishment of left atrial-left ventricular continuity. Thus, as with the univentricular hearts, the best chance of success, if any success is possible, seems to lie in atrial septectomy, construction of a new atrial septum, and use of the modified Fontan procedure. The aorta would then receive pulmonary venous blood via the right ventricle and the ventricular septal defect. As with the majority of hearts in our series, the possibility of success of such a procedure is highly speculative.

The above emphasises that in most instances our practice of dividing left atrioventricular valve atresias into the morphological categories of absent connection and imperforate valve confers little practical clinical value. The entity is coloured most strongly by the lack of egress from the left atrium whatever its anatomical substrate. None the less, recognition of the different morphological possibilities is of significance in determining the possible surgical options as in our one case where a modified Fontan procedure was feasible. Equally, though we have yet to see such a case, hearts may be encountered in which an imperforate membrane is of sufficient size to justify its surgical removal and replacement with a prosthetic valve. Then it would be essential to distinguish the presence of the membrane.

At present, it can be said that cases of left atrioventricular valve atresia in the presence of a patent subaortic outflow tract can be palliated with an acceptable degree of success. Whether more "corrective" procedures will become available for these palliated patients remains to be established, but at least in our experience the palliation in itself has provided an acceptable quality of life.

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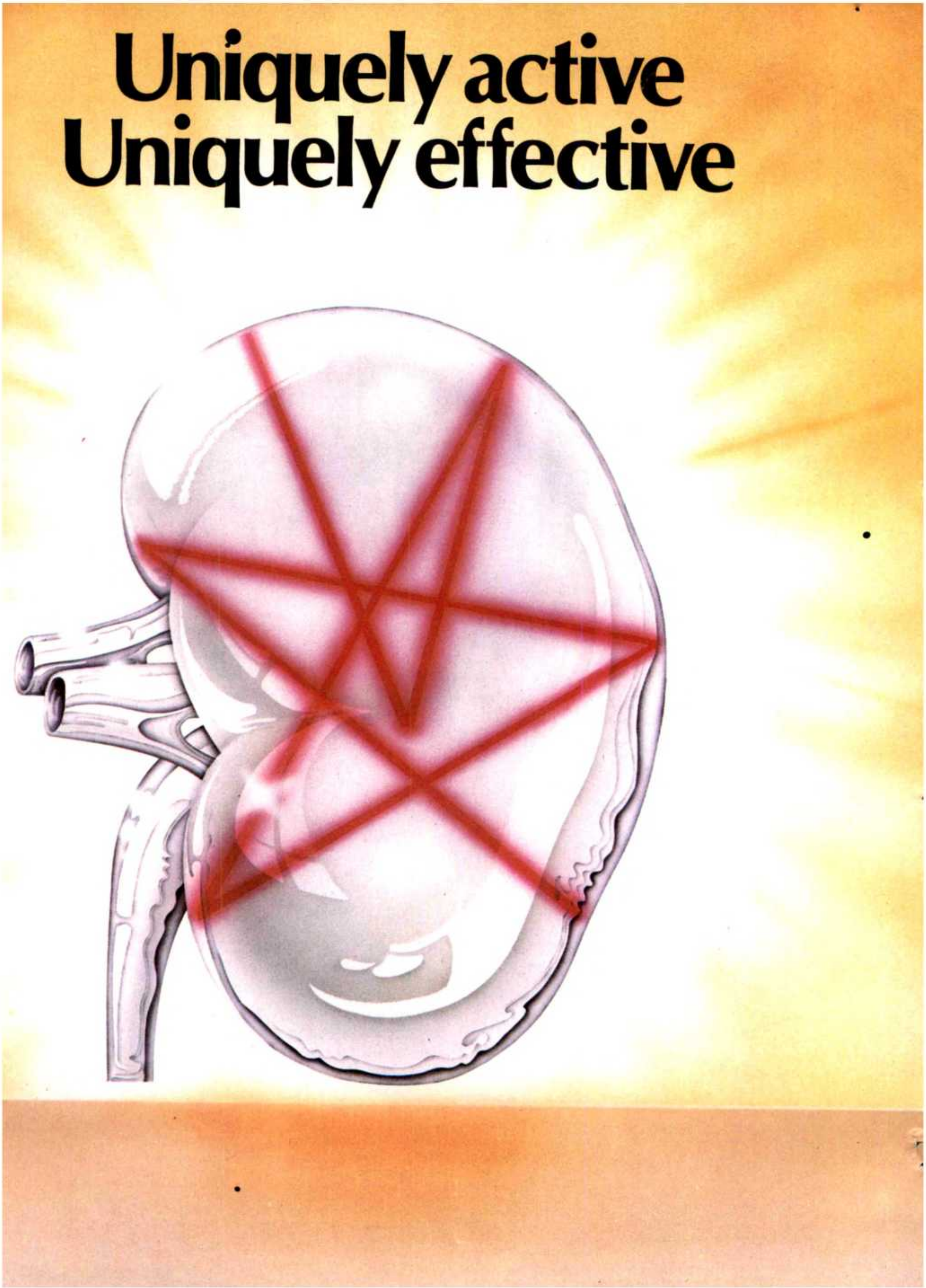
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For patients with accelerated or malignant hypertension, who are unresponsive to conventional therapy, it may be necessary to increase the daily dose of Capoten (captopril) every 24 hours, until a satisfactory blood pressure response is obtained or the maximum dose of Capoten is reached.
When Capoten (captopril) is used alone, concomitant sodium restriction may be advantageous. Capoten may be used in conjunction with other antihypertensive agents, particularly thiazide diuretics and beta-blockers.

Patients with Renal Impairment An average of about 75% of a given daily dose of captopril is usually excreted in the urine; captopril retention occurs in the presence of impaired renal function. The dosage interval should be increased as follows when creatinine clearance is below 75ml/min/1.73m^2:

Creatinine Clearance (ml/min/1.73m^2)	Dosage Interval (Hours)
>75	8
75 – 35	12 – 24
34 – 20	24 – 48
19 – 8	48 – 72
7 – 5	72 – 108 (3 to 4.5 days)

When concomitant diuretic therapy is required, a loop diuretic (e.g. frusemide) is preferable to a thiazide diuretic.

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Hypotension A precipitous reduction of blood pressure may occasionally occur within the first three hours following the initial dose of Capoten in patients on diuretics, on a low sodium diet or undergoing dialysis. An exaggerated hypotensive effect may also occur with one or two subsequent doses. Medical supervision should be maintained for one hour after the initial dose. This transient hypotensive response is not a contra-indication to further doses which can be given without difficulty once blood pressure has increased after volume expansion.

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Changes in Renal Function Some patients with renal disease, particularly those with renal artery stenosis, have developed increased serum concentrations of BUN and serum creatinine after reduction of blood pressure with Capoten, usually along with a diuretic. Capoten dosage reduction and/or discontinuation of diuretic may be required. For some of these patients, it may not be possible to normalise blood pressure and maintain adequate renal perfusion.

Pregnancy The safety of Capoten in pregnancy has not been established; therefore, Capoten should be given during pregnancy only if the potential benefit justifies the potential risk to mother and foetus.

Nursing Mothers Caution should be exercised when Capoten is administered to a nursing mother.

Surgery/Anaesthesia In patients undergoing major surgery, or during anaesthesia with agents which produce hypotension, Capoten will block angiotensin II formation secondary to compensatory renin release. This may lead to hypotension which can be corrected by volume expansion.
Capoten may cause a false-positive urine test for acetone.

Side Effects Neutropenia/Agranulocytosis Proteinuria see warnings. Skin rashes and taste disturbance have been reported. Gastric irritation and abdominal pain may occur.

Other Paraesthesias of the hands, serum sickness, cough, bronchospasm and lymphadenopathy have been reported. Hypotension – see Warnings. Tachycardia has been observed in a few volume depleted patients.

Overdosage In the event of overdosage, hypotension would be the most important problem. Volume expansion with an intravenous infusion of normal saline is the treatment of choice for restoring the blood pressure to normal. Captopril is removed by dialysis.

PACKAGE QUANTITIES

In bottles of 100

Basic NHS Price 25mg tablets 100 – £21.40

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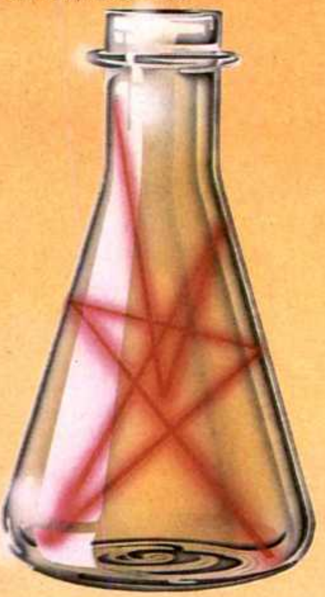

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Br Heart J 1982; **47**: 41-3

Balloon atrial septostomy under two dimensional echocardiographic control

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SUMMARY Two dimensional echocardiography has been used to guide balloon atrial septostomy in five cases of transposition of the great arteries. A single lumen balloon catheter was used. The catheter can be accurately located within the left atrium before inflation of the balloon, thus avoiding some of the traumatic accidents possible during septostomy. The balloon can be observed creating the atrial defect and the approximate size of the resulting defect noted. It can also be seen if the foramen ovale is only being stretched and not torn. The use of the two dimensional echocardiogram during septostomy should significantly contribute to the speed, efficiency, and safety of the procedure.

Transposition of the great arteries is one of the most common cyanotic congenital heart diseases, affecting about one in 4000 live births.[1] Before the introduction of surgical techniques to increase atrial mixing the mortality rate from transposition was high, 95% of cases dying by the end of the second year of life, approximately 40% of those in the first month.[2] Surgical septectomy improved this situation vastly[3] but there was still a very high mortality in the first three months of life. This led to the introduction of balloon septostomy.[4] This palliative procedure allows the patient to survive until the appropriate time for corrective surgery.[5] There is, however, a remaining small mortality which is directly attributable to technical failure of balloon atrial septostomy. The reasons for technical failure include failure to introduce the balloon catheter,[6] failure of adequate septostomy,[7] and traumatic damage caused by the balloon to structures other than the atrial septum. Atrial perforation and tricuspid valve perforation[6 7] have both been reported. Failure of balloon atrial septostomy varies between seven in 43 in an early series[6] to two in 44 in a more recent series.[8] Some of this improvement in mortality is because traumatic damage to other structures has been avoided by careful positioning of the balloon before each "pull". The exact position of the balloon using x-ray screening alone is not always clear. The use of a double lumen balloon catheter allows chamber pressure to be recorded, thus eliminating the danger of inflating the balloon in a ventricular chamber. In addition, careful slow inflation of the balloon should ease the catheter out of a pulmonary vein or the left atrial appendage if it is wrongly positioned there.

Two dimensional echocardiography can be used to locate and position the balloon catheter. We have used this in five cases of transposition of the great arteries and feel this technique contributes significantly to the speed, efficiency, and safety of the septostomy procedure.

Subjects and methods

Five consecutive cases of suspected transposition of the great arteries were studied by two dimensional echocardiography. An Advanced Technical Laboratories Mark III Sector Scanner was used with a 5 MHz transducer. The age range of the patients was from 1 day to 8 months (see Table). The diagnosis was confirmed by echocardiography in each case, being transposition and ventricular septal defect in four

Table *Size of atrial septal defect created*

Case No.	*Age*	*Diagnosis*	*Approximate size of ASD created (cm)*
1	2 wk	TGA, VSD	0·6
2	2 d	TGA, VSD	0·6
3	8 mth	TGA, VSD	None
4	1 d	TGA	0·5
5	2 d	TGA, VSD	0·5

TGA, transposition of great arteries; VSD, ventricular septal defect; ASD, atrial septal defect.

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*British Heart Foundation Junior Research Fellow.

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patients and transposition with intact septum in one. Cardiac catheterisation was performed and the haemodynamic assessment made. A single lumen Edwards Laboratories balloon septostomy catheter was introduced into the right saphenous vein. The echocardiograph transducer was positioned in the subcostal region to visualise the right atrial/inferior vena caval junction. The catheter was then advanced using screening until it was seen on the echocardiogram entering the right atrium. The atrial septum and foramen ovale were then identified echocardiographically and the catheter was passed through the foramen ovale to the left atrium under echocardiographic control without recourse to *x*-ray screening. The position of the balloon was confirmed by inflation with 0·5 ml saline. The balloon was then fully inflated while being directly observed and then withdrawn across the atrial septum. The balloon could be monitored and recorded during each septostomy procedure (Fig. 1a and b). The approximate size of the defect created by the balloon during and at the end of the procedure could be estimated (Fig. 2a and b).

Discussion

The use of two dimensional echocardiography before catheterisation in a sick neonate greatly facilitates the catheterisation study. If a diagnosis of transposition of the great arteries is made it is only necessary to acquire confirmatory haemodynamic data at catheterisation and perform the balloon atrial septostomy as quickly as possible. This is particularly important if the infant's condition is poor. In our experience the use of the two dimensional echocardiogram during catheterisation can further expedite the procedure.

The single lumen catheter is smaller than the double lumen version and thus easier to introduce. One of the technical causes of failure may thereby be avoided. The ability of the cross-sectional echocardiogram to identify accurately the position of the balloon within the heart means that the extra margin of safety provided by the double lumen catheter when using *x*-ray screening alone is no longer required. The position of the actual tip of the catheter is sometimes difficult to determine. Once the catheter has adopted a curved course the echocardiographic plane may cut the catheter proximal to the tip, the tip itself being out of the plane of section. Partial inflation of the balloon, however, will always allow identification of the catheter tip. In addition, direct visualisation of the foramen ovale or atrial septal defect facilitates the positioning and repositioning of the catheter in the left atrium, rendering the procedure simple and quick to perform. Our standard technique of between eight to 10 "pulls" was performed in each case without the need for *x*-ray screening during the procedure. In case 3 it

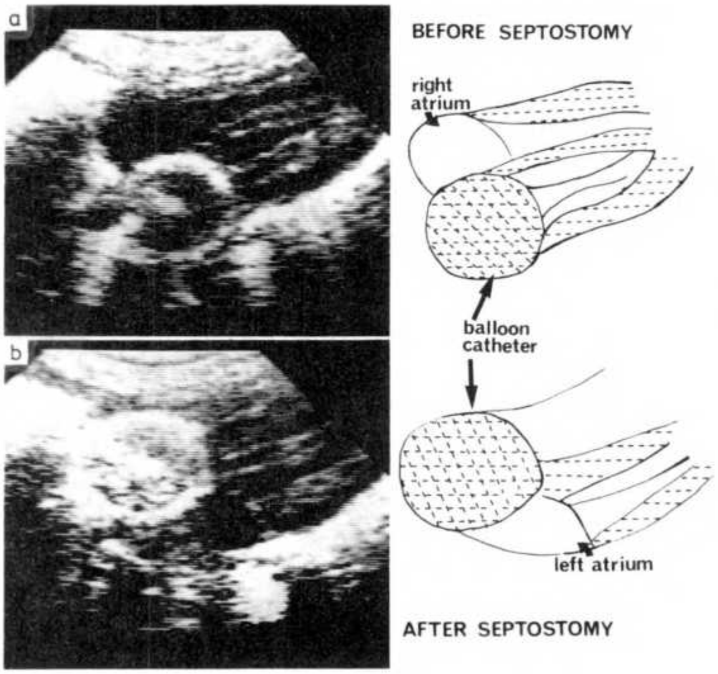

Fig. 1 *The subxiphoid four chamber section of the heart is visualised on the echocardiogram. (a) The inflated balloon catheter is seen within the left atrium before septostomy; (b) the balloon is seen within the right atrium after septostomy.*

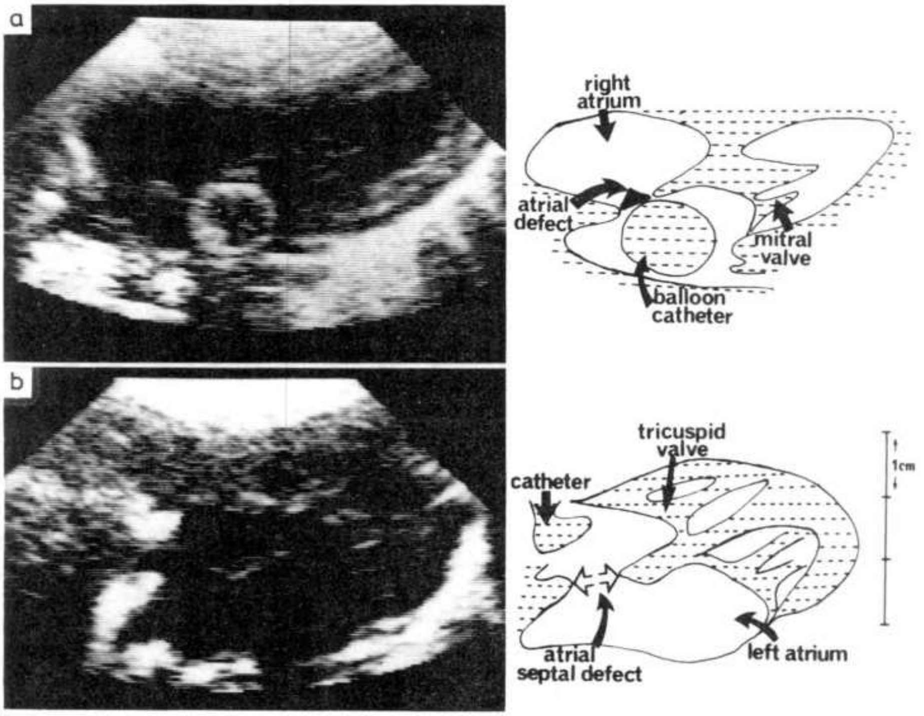

Fig. 2 *(a) The balloon catheter, partially inflated, can be seen in the left atrium resting on the torn atrial septum; (b) the deflated balloon catheter is now in the right atrium after septostomy has been performed eight times. The approximate size of the defect can be measured.*

appeared that the balloon was being compressed as it passed across the atrial septum and that no defect had been created.

A surgical septectomy was therefore performed in this patient. In cases 1, 2, 4, and 5 the size of the defect created appeared to be approximately 0·5 cm.

Using echocardiographic control it should be impossible to position the catheter incorrectly, and therefore injuries inflicted on withdrawal such as tricuspid valve damage or perforation of the left atrial-pulmonary vein junction may be completely avoided.

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Myocardial infarct size and cardiac performance at exercise soon after myocardial infarction*

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SUMMARY Infarct size was estimated from serial serum CK MB measurements in a series of 101 patients admitted less than 15 hours after the first acute myocardial infarction. A maximal symptom limited exercise test comprising impedance measurements for the estimation of stroke volume at rest and at different levels of exercise was performed early after admission by 26 patients.

There was a slight, though not significant, negative correlation between infarct size and physical capability as measured by the duration of work. The rise in systolic blood pressure during exercise showed a significantly negative and the increase in heart rate a significantly positive correlation to infarct size. This suggests that the rise in blood pressure, which is less in patients with the larger infarcts, is compensated by an increase in heart rate, so that the same maximum of cardiac performance and myocardial oxygen consumption is reached. The increase in cardiac stroke volume during exercise was negatively correlated with infarct size. Stroke volume only increased during lower levels of exercise; the increase in cardiac output at higher levels of exercise was achieved entirely by an increase in heart rate. The magnitude of ST segment elevation during exercise showed a significantly positive correlation with infarct size, whereas the occurrence of arrhythmias during exercise was independent of it.

The extent of myocardial injury in acute myocardial infarction and its possible impact on the subsequent course of the disease have attracted much attention in recent years. Hence, in vivo estimation of infarct size has become of importance, and various methods of estimation have been applied.[1]

Some studies after acute myocardial infarction have investigated the relation between the estimated infarct size and cardiac performance, measured either as the ejection fraction of the left ventricle by radionucleocardiography,[2 3] or through the pulmonary haemodynamics at right heart catheterisation.[4] The exercise test provides information about several aspects of cardiac performance, and is applicable also during the first weeks after acute mycocardial infarction. There are no reports, however, of a comparison between the results of exercise tests and the estimated infarct size in a large series of patients.

Exercise tests three weeks after acute myocardial infarction have been routine at our unit since January 1972.[5] Moreover, in recent years estimation of the infarct size from serum levels of creatine kinase isoenzyme MB (CK MB) has shown a satisfactory correlation with anatomical measurements taken at necropsy.[6] In this study the estimated infarct size and the results of exercise tests, usually carried out three weeks after the onset of acute myocardial infarction, were compared in a series of patients with the first infarct.

Patients

We investigated a series of patients with acute myocardial infarction who met the following criteria: no previous history of acute myocardial infarction, duration of infarct less than 15 hours, sufficient data for estimating the infarct size from serial enzyme measurements, and ability to do an exercise test according to our standard procedure. The patients were taken out of all admissions to our coronary care unit during the course of 12 months. As all cases of suspected acute myocardial infarction without excep-

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tion are admitted to the coronary care unit and as deliberate treatment of such infarction in the home is rare in Denmark, we believe that our population is representative of virtually all those who survive an acute myocardial infarction long enough to reach hospital.

Between 1 June 1978 and 1 June 1979 the coronary care unit received 393 patients with acute myocardial infarction, defined according to the criteria given below. The duration of the infarct was less than 15 hours in 345, and sufficient data for calculating the infarct size from determinations of the serum CK MB were available in 321. Acute myocardial infarction had occurred for the first time in 225 patients. Twenty-eight died during admission and 197 were discharged from the coronary care unit after an observation period of slightly less than three weeks. Out of these 197 patients, 96 were unable to perform the exercise test for the reasons stated in Table 1. These were 64 men between 48 and 93 years of age (mean 67·2 years) and 32 women between 46 and 83 years of age (mean 68·1 years).

Table 1 *Reasons for non-performance of exercise test soon after acute myocardial infarction*

Reasons	*No.*
Heart failure, pronounced	8
Hypertension, pronounced	4
Angina pectoris, severe and persistent	4
Atrioventricular block, treated with temporary pacemaker	3
Intermittent bundle-branch block	2
Postinfarction syndrome	1
Pulmonary conditions (bronchial asthma, pulm. embolism, pneumonectomy, etc.)	4
Intermittent claudication	9
Gangrene of foot	1
Joint disorders	9
Paralysis of extremity	10
Urethral catheter	2
Blindness	1
Other medical disorders (jaundice, dyspepsia, epilepsy)	4
Age and/or poor general condition	20
Refusal to participate	10
Unable to bicycle	2
Lack of laboratory staff	2
Total	96

Thus, our study group comprises 101 patients who survived the first acute myocardial infarction, who were able to do the exercise test, and in whom the infarct size could be estimated. There were 88 men between 23 and 81 years of age (mean 54·6 years) and 13 women between 42 and 73 years of age (mean 56·2 years). As was to be expected, there was a predominance of men and of somewhat younger people who were able to perform the test.

Methods

Acute myocardial infarction was defined by the occurrence of typical clinical symptoms and/or typical evolution of electrocardiographic abnormalities, when confirmed by a temporary rise in serum CK MB levels.[7] Electrocardiograms in six praecordial and three extremity leads were recorded daily. Blood samples were drawn on admission, and approximately every eight hours thereafter until the CK MB values were normal. CK was analysed according to the Scandinavian recommended methods, and CK MB was determined by electrophoresis on agarose gel followed by fluorescence scanning.[8] The interassay variation of the technique is below 10% in the lower and below 5% in the higher range of activity.

Infarct size was calculated from the serum CK MB values, according to a method described elsewhere,[9] and expressed in U/l.

Eighty-six patients performed the exercise test according to the standard procedure of the unit, that is during the third week after the onset of the acute myocardial infarct and a few days before discharge from hospital. The test was postponed in the case of 15 patients: in four to week four, in five to week five, in three to week six, in one to week seven, and in two to week eight. The reasons were reinfarction or progression of the first infarction on the fourth day (one patient), complicating thrombophlebitis (one patient), and lack of laboratory staff over the Christmas holidays, etc. (13 patients).

At the beginning of the test the patients rested supine for at least 10 minutes, while self-adhesive electrocardiograph electrodes were placed in the deltoid regions, in the groins, and on the chest positions at V1-V4-V6, and a blood pressure cuff was placed round the upper arm.[5]

During the test the stroke volume in some of the patients could be calculated repeatedly from measurements of variations in thoracic impedance: two mylar bands were placed around the neck and two around the lower thorax, and a microphone was placed in the aortic area, all connected to the IFM/Minnesota Impedance Cardiograph Model 304 A.

The graded exercise was done on a bicycle ergometer with electronically controlled braking (Siemens-Elema A.M. 368), the load being increased in stages from 50 to 100 to 150 watts, remaining at each stage for six minutes in order to ensure a steady state. The aim was a maximal, symptom limited performance, and the patient was encouraged to proceed until he reached the limit set by such physiological symptoms as fatigue and dyspnoea. The reasons for stopping the exercise were pathological symptoms, such as anginal or leg pain; objective signs, such as pronounced and rapidly increasing changes in the ST segment, extrasystoles, especially when multiform or appearing in series or close to the preceding T wave; and either a rapid rise in blood pressure to very high values, or the absence of a rise in blood pressure.

Electrocardiograms in three extremity leads and three praecordial leads and heart rate were recorded continuously, and blood pressure was measured every minute throughout the test. All measurements were continued through the following periods: supine at rest for at least three minutes, sitting on the bicycle at rest for three minutes, sitting on the bicycle during exercise, and sitting on the bicycle at rest for 10 minutes after exercise.

In the electrocardiograms any ST segment deviation from the level of the PR segment to the TP segment was measured 0·06 second after the nadir of the last wave of the QRS complex.

Rhythm disturbances were assessed before exercise (at least three minutes supine plus three minutes sitting on the bicycle) and from the continuous electrocardiographic recording during the entire period of exercise and for 10 minutes after.

In those patients prepared for impedance measurements, the dZ/dt curve was recorded by an electrocardiograph writer (Mingograph 34, Elema), simultaneously with one unipolar chest lead of the electrocardiograph, and a phonocardiogram from the aortic area. The stroke volume was calculated according to Kubicek *et al.*,[10] through 10 cardiac cycles at the end of the following periods: supine at rest, sitting at rest, at each increase in exercise load, and 10 minutes after cessation of exercise.

Statistical calculations were made by the rank test for unpaired data (Mann-Whitney test). The t test was used for testing if the coefficients of correlation were different from zero.

Results

Exercise was discontinued in the 101 patients for the reasons given in Fig. 1. Two-thirds, or 67 patients, were able to continue exercise until extreme fatigue and dyspnoea set in, three stopped mainly because of nervousness, and 17 were stopped by anginal pain. In only 14 cases was the exercise interrupted by the investigator: in four because of frequent, but always single ventricular extrasystoles; in three because of the development of very pronounced ST deviation; in one because of an insufficient rise in blood pressure; and in six because of a rapid and unacceptably high rise in blood pressure. In all cases, the rhythm disturbance or electrocardiographic abnormalities disappeared or the blood pressure approached initial values within a few minutes after stopping exercise. More severe arrhythmias, persistent electrocardiographic abnormalities, signs of reinfarction, or other serious complications did not occur.

Fig. 1 also shows the performance of work which ranged from two minutes of exercise at 50 watts to 21 minutes at the phased increase in load from 50 to 100 to 150 to 200 watts, remaining at each load for six minutes. Among the 67 patients who continued exercise until the physiological limit set by fatigue and dyspnoea, the median exercise duration was 12·0 minutes (quartiles 8 and 14 minutes). Within this group of 67 the 14 who received digitalis and/or a beta-blocking agent had a significantly lower capacity of work (median 8·5 minutes) when compared with the rest (median 12·0 minutes, p=0·03).

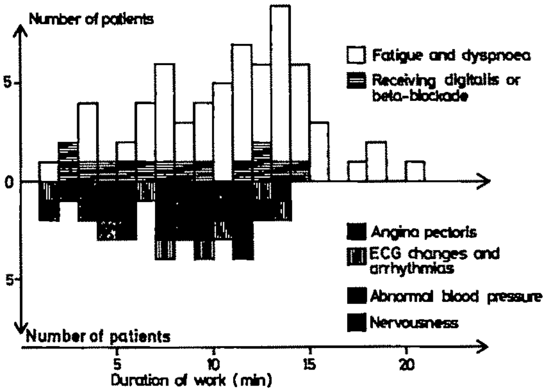

Fig. 1 *Performance during exercise testing on a bicycle ergometer at 50 watt for 6 minutes + 100 watt for 6 minutes + 150 watt for 6 minutes, etc., in 101 patients, 15 to 53 days (median 17 days) after the onset of their first acute myocardial infarct. Above the horizontal line: the performance of 67 patients continuing exercise until intolerable fatigue and dyspnoea. Below the line: 34 patients who stopped exercise for other reasons.*

Patients whose exercise was stopped by the investigator, because of electrocardiographic abnormalities, or arrhythmias, or abnormal blood pressure response, and those who stopped because of anginal pain, had a significantly lower capacity of work than the patients who stopped exercise only because of fatigue and dyspnoea (p=0·03, and p=0·01).

Table 2 shows the relation between the estimated infarct size and duration of work for the 53 patients who had not had digitalis or beta-blockers and who continued exercise until the limit of physiological fatigue and dyspnoea. The median infarct size in this group was 756 U/l; range 60 to 2973 U/l, corresponding roughly to between 3 g and 140 g of infarcted tissue.[6] There was only a slight, statistically

Table 2 *Relation between estimated infarct size, duration of work, and age (n=53)*

	r	*SEE %*	*p*
Infarct size vs. duration of work	−0·15	30	0·25
Age vs. infarct size	−0·36	26	0·004
Age vs. duration of work	−0·42	32	0·002

insignificant, negative correlation between infarct size and duration of work. We found, however, a significantly negative correlation between age and infarct size. As there was also a strong negative correlation between age and work performance, the influence of age tends to veil the negative correlation between infarct size and work performance.

Table 3 shows the relation between the estimated infarct size and the response in systolic blood pressure and heart rate during exercise. A significantly negative correlation was found between the infarct size and the rise in systolic blood pressure, whether the latter was understood as the absolute maximum reached in 53 patients, or as the rise from sitting at rest to exercising at 100 watts in 48 patients. A significantly positive correlation was found between the infarct size and the increase in heart rate, as regards the absolute maximal values and the rise from resting to maximal exercise values. As these two correlations cancelled each other, the pressure rate product showed no significant correlation to infarct size.

Table 3 *Relation between estimated infarct size and response to exercise test*

		Infarct size (CK MB U/l)			
		No.	*r*	*SEE %*	*p*
Systolic blood pressure	Max. value	53	−0·32	9	0·02
	Rise*	48	−0·46	24	0·01
Heart rate	Max. value	53	0·39	11	0·004
	Rise*	48	0·39	30	0·004

*Expressed as the difference between the steady state value of work load 100 W and the resting value, both while sitting on the bicycle.

In Fig. 2 the estimated infarct size is related to the maximal increase in stroke volume index and cardiac index, as estimated from the variations in thoracic impedance during exercise. The maximal increase in stroke volume index and in heart rate was measured as the difference between the maximal value during exercise and the value measured when sitting on the bicycle just before starting exercise. The resting values of the stroke index and heart rate showed no significant correlation with the infarct size. There was, however, a significantly negative correlation between the infarct size and the rise in stroke index (p=0·01), and in cardiac index (p=0·03). As regards the increase in stroke index, the range of results was broad in the patients with the smallest infarcts whereas it was low in those with larger infarcts. We did not find the combination of a large infarct size and a high increase in stroke volume during exercise. Stroke index did not increase at all in four patients during exercise, but, because of increased heart rate, the cardiac index rose in all 26 patients.

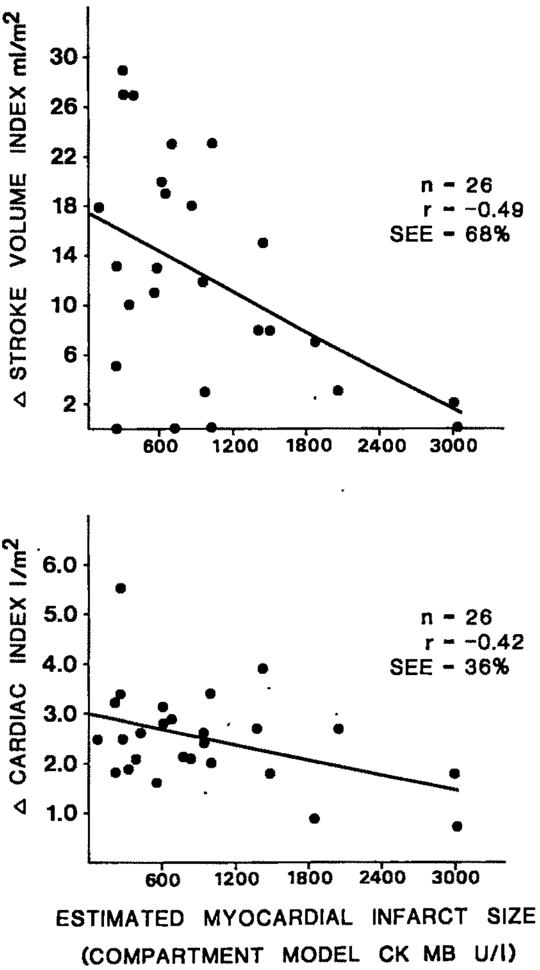

Fig. 2 *Relation between the estimated myocardial infarct size and increase in stroke volume index (above, p=0·01) and in cardiac index (below, p=0·03) during exercise calculated from impedance measurements.*

Fig. 3 shows the values in 26 patients of stroke volume, heart rate, cardiac output, and rate-pressure product at five points of the exercise test: resting supine, resting sitting on the bicycle, after six minutes work at 50 watts, after 12 minutes work at 50 to 100 watts (in the 23 patients who were able to continue 12 minutes of work), and 10 minutes after cessation of exercise still sitting on the bicycle. At rest before exercise the transition from supine to sitting position was followed by a considerable decrease in the stroke volume and only a small increase in heart rate, and consequently a distinct drop in the calculated cardiac output. During the first six minutes of exercise,

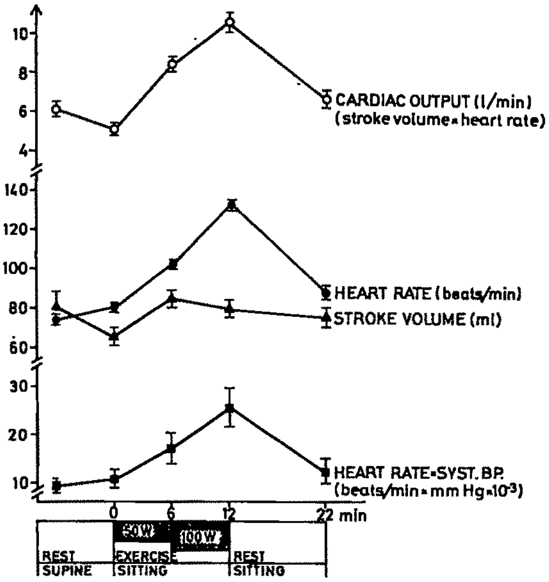

Fig. 3 *Mean value ± standard error of the mean of stroke volume, heart rate, cardiac output (as the product of stroke volume and heart rate), and the product of heart rate and systolic blood pressure, all measured at the same five points of the exercise test. See text.*

Table 4 *Estimated myocardial infarct size and changes in ST segment during exercise (see text)*

	No.	*Infarct size (CK MB U/l)*		
		Median	*Quartiles*	*p*
No ST elevation ≥ 1 mV	35	730	349-1315	0·05
ST elevation ≥ 1 mV	18	1087	650-2341	
Total	53			
No ST depression ≥ 1 mV	31	756	490-1726	0·61
ST depression ≥ 1 mV	22	891	380-1840	
Total	53			

stroke volume and heart rate rose and cardiac output was much increased. At the higher levels of exercise up to the maximal performance, stroke volume remained constant or even decreased again, so that the further rise in cardiac output was caused only by increased heart rate. Comparison with the infarct size calculated in each patient showed a significantly negative correlation between that and the rise in stroke volume during the first level of exercise ($r = -0{\cdot}33$, $p = 0{\cdot}03$), but no correlation between infarct size and the variation in stroke volume after the first six minutes of exercise ($r = -0{\cdot}11$, NS). The pressure-rate product was increased two-and-a-half times on average during exercise, but, as mentioned, this increase showed no correlation to the infarct size.

Table 4 shows the relation between the infarct size and deviations of the ST segment during exercise in the 53 patients who continued exercising until stopped by dyspnoea and fatigue. No correlation could be shown between the infarct size and depression of ST segment during exercise, but a barely significant positive correlation was found between the infarct size and ST elevation during exercise. The median infarct size was 730 U/l for those without ST elevation, 784 U/l in 12 patients with ST elevation of 0·1 or 0·2 mV, and 2210 U/l in six patients with ST elevation larger than 0·2 mV. The difference between the two subgroups was not statistically significant. Among the 18 patients with ST elevation during exercise, 13 had an anterior infarction and five an inferior infarction.

Of the 17 patients who were stopped by angina pectoris during the exercise test, an ST deviation was absent in two but present in 14, and 0·2 mV or more in 10 of these, the deviation being an ST depression in nine and an ST elevation in five. The median infarct size was significantly smaller in the 17 patients when compared with the 53 patients who stopped because of fatigue and dyspnoea (median 363 U/l, versus 756 U/l, $p = 0{\cdot}03$).

During observation before exercise, rhythm disturbances were present in 13 of the 101 patients, namely ventricular extrasystoles in nine, supraventricular extrasytoles in two, and atrial fibrillation in two. Arrhythmias increased in all 13 patients and occurred in another 41 patients during exercise. Thus, 54 patients presented arrhythmias during exercise, in 44 of them as ventricular ectopic beats. There was, however, no significant connection between the infarct size and the manifestation or exacerbation of either ventricular or supraventricular arrhythmias during the exercise test.

Discussion

The size of a myocardial infarct, as calculated from serial determinations of blood levels of the cardiospecific enzymes, has shown a good correlation with the nitro-BT stained infarct size measured at necropsy.[4 6] The calculated infarct size has been found to be of negative importance in the functional classification of patients after acute myocardial infarction[11] and in their life expectancy.[12]

Several studies have shown exercise testing three weeks after acute myocardial infarction to be safe. The test also provides important information on the capability of the diseased heart, and on the short-term and long-term prognosis after an acute infarction. Thus the increase in stroke volume, systolic blood pressure and oxygen consumption has been found to be smaller and the rise in heart rate higher in patients with a previous history of acute myocardial infarction than in those with ischaemic heart disease without such infarction[13] and than in normal subjects.[14] Moreover, the occurrence of ST depression and anginal pain and a smaller rise in the pressure-rate product at exercise have been found to indicate a relatively poor prognosis.[15 16] In another series, impaired cardiac pump function and clinical signs of congestive heart failure were clear signs of a deteriorated prognosis after acute infarction.[17]

Reports on the correlation between estimated size of the myocardial injury and cardiac performance soon after an acute myocardial infarction have been few. Paine *et al.*[18] investigated 100 patients several months after infarction with an equal share of one-, two-, and three-vessel disease at coronary arteriography. They found a significantly positive correlation between duration of exercise and left ventricular ejection fraction at angiography, a significantly negative correlation between duration of exercise and scar size estimated at angiography, and a larger ST segment elevation during exercise in patients with lower ejection fraction and larger angiographic scar size. In 50 patients with acute myocardial infarction Bleifeld *et al.*[4] found a negative correlation between infarct size calculated from serial CK determinations and left ventricular performance estimated from cardiac index and pulmonary end-diastolic pressure at right heart catheterisation.

In the present study of 101 patients infarct size calculated from blood enzyme levels showed a slight but insignificant negative correlation with physical capability, as measured by the duration of work at exercise soon after acute mycocardial infarction in the 53 patients (mean age 53·9±11·1 years) who were able to continue exercise until stopped by fatigue and dyspnoea. This correlation has the same tendency, but is not so pronounced, as the one which Paine *et al.*[18] found in somewhat younger patients (mean 48 ± 8 years) several months (median 4·5, mean 13±4 months) after acute myocardial infarction. As scar size angiocardiography has shown a very good correlation with infarct size calculated from serum CK MB levels,[2] the reason for the quantitative differences between the two series might possibly be found in the different time span from acute infarction to the exercise test. Cardiac performance soon after acute infarction is presumably more uniformly depressed, and patients with a smaller infarct size are probably able to regain some of their physical capability in subsequent months.

In the present series systolic blood pressure and heart rate at rest were not related to infarct size, but the rise in systolic blood pressure during exercise showed a significantly negative correlation, and the increase in heart rate a significantly positive correlation, so that the rise in the pressure-rate product, and presumably the rise in myocardial oxygen consumption, remained unrelated to infarct size. The rise in systolic blood pressure during exercise seems to be lower in patients with larger infarcts, but a higher increase in heart rate compensates, thus bringing about the same myocardial oxygen consumption and cardiac performance.

Calculations of cardiac stroke volume from measurements of thoracic electrical impedance have shown a very good correlation with results from the dye dilution method (r=0·90), both at rest and at exercise.[19]

In the present series, the resting values of stroke volume and cardiac output, as calculated from impedance measurements, were essentially the same whether the infarcts were large or small, but the rise during exercise was to a significant extent negatively correlated with infarct size. Repeated measurements during the exercise test showed that stroke volume rose only at the lower levels of exercise, and that it remained unchanged at higher levels, the further rise in cardiac output being achieved entirely by an increase in heart rate. In some patients, both with large and small infarcts, the stroke volume did not increase at all during exercise; the total rise in cardiac output was achieved by an increase in heart rate. These findings tend to support the impression that treatment with a beta-blocking agent might not be suitable for patients with larger infarcts. When patients changed from a supine position to sitting on the bicycle, stroke volume and cardiac output fell considerably, nearly as much as the subsequent rise in stroke volume during exercise. It is not known, however, how much of this decrease reflects the well-known orthostatic reduction in stroke volume, or how much might be changes in thoracic impedance simply because of the anatomical alterations from lying to sitting.

Depression of ST segments during exercise occurred in slightly over one-half of the patients with angina pectoris, and in two-fifths of those without angina pectoris, with no significant correlation with infarct size. Elevation of the ST segment, however, occurring in slightly less than one-third of the patients *with* and one-third of the patients *without* anginal pain showed a significantly positive correlation with infarct size. These observations are in accordance with earlier findings that exercise induced ST elevation is related to the extension of the akinetic myocardium after acute infarction.[20]

It is noteworthy that the 17% of the patients who experienced angina pectoris during exercise had significantly smaller infarcts, probably indicating an inverse relation between the extent of the infarcted and of the jeopardised myocardium.

Previous studies[21] have found that the occurrence of ventricular arrhythmias during the hospital phase of acute myocardial infarction was positively correlated to infarct size. The frequency of rhythm disturbances before and during exercise is much the same as that found in earlier series in our coronary care unit,[5,16] and by others using a symptom limited exercise test early after acute myocardial infarction;[22] the frequency is somewhat higher than in series with preset limits for cardiac performance in this group of patients.[23,24]

In the present series, no significant correlation could be shown between infarct size and any kind of arrhythmia before or during exercise.

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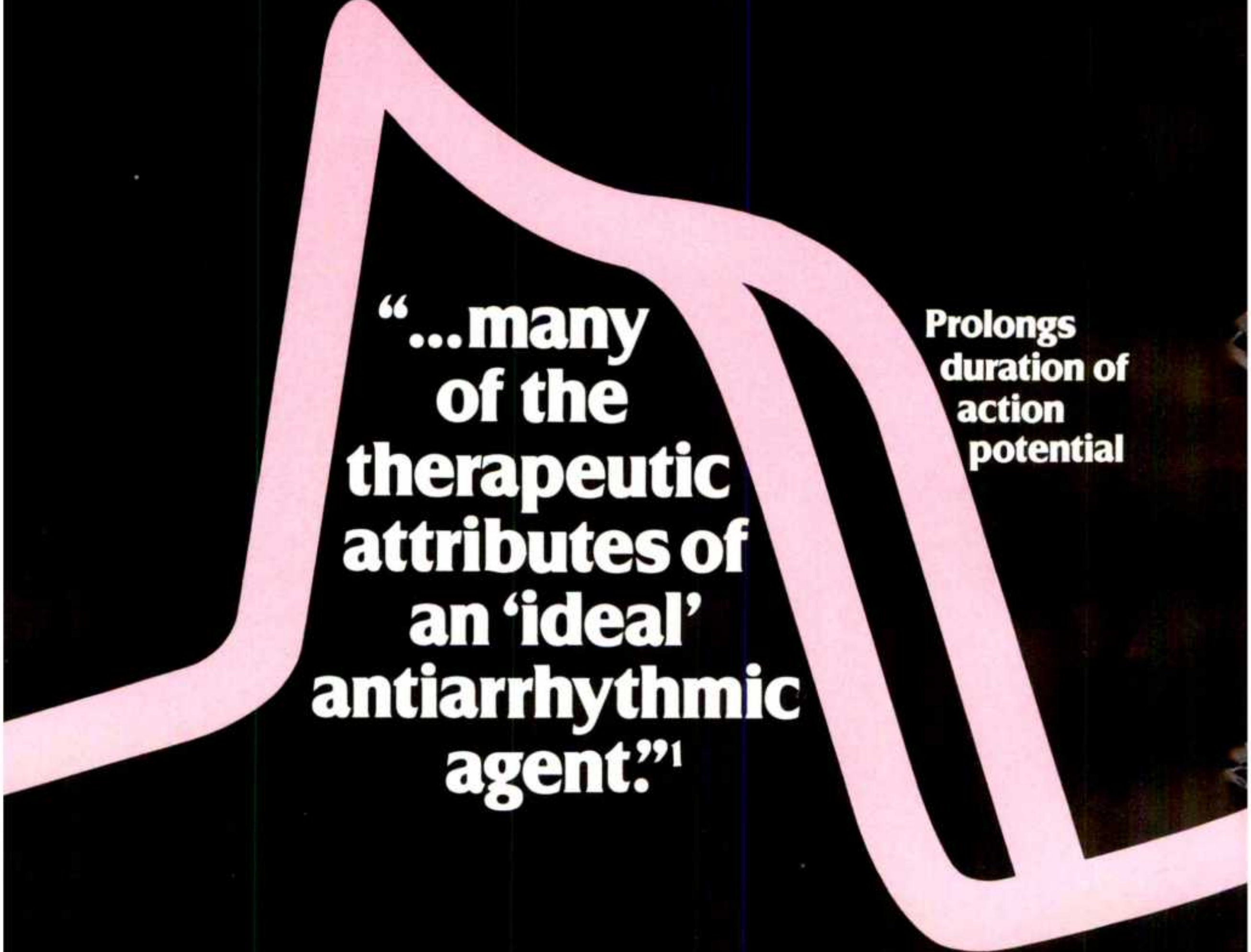

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Myocardial injury after phenylpropanolamine ingestion*

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SUMMARY Three patients developed clinical evidence of myocardial injury after acute ingestion of phenylpropanolamine, a sympathomimetic amine found in a large number of decongestant and appetite suppressant formulations. Increases in the serum creatine kinase and MB isoenzyme levels, ventricular arrhythmias, and electrocardiographic repolarisation abnormalities were seen. Excessive catecholamine stimulation has been shown to produce acute myocardial necrosis experimentally, and a similar mechanism may be present in these patients.

Phenylpropanolamine is a sympathomimetic amine used widely as a decongestant and appetite suppressant. It is freely available either over the counter or on prescription, usually in combination with other drugs. The effects of phenylpropanolamine are largely the result of alpha-adrenergic agonist activity resulting from both direct stimulation of adrenergic receptors and release of neuronal norepinephrine.[1] The principal adverse effect of phenylpropanolamine is dose related hypertension[2 3] and ventricular arrhythmia has been described.[4] Studies in rats have shown that sympathomimetic amines can cause myocardial necrosis,[5] but evidence of this in humans after the acute ingestion of sympathomimetic amines has not been previously reported.

We describe three patients seen within four months who developed clinical evidence of myocardial injury after acute phenylpropanolamine ingestion, including an increase in the MB isoenzyme of creatine kinase and electrocardiographic abnormalities.

Case reports

CASE 1

A 24-year-old woman was admitted with chest pain three hours after ingesting a single capsule of phenylpropanolamine 50 mg, chlorpheniramine 4 mg, and belladonna alkaloids 0·2 mg. Dyspnoea, headache, blurred vision, and nausea were present. There was no history of cardiovascular disease, hypertension, or ingestion of other drugs.

Blood pressure was 204/148 mmHg and pulse rate 112. She was confused and restless. The cardiovascular and respiratory systems and the fundi were normal. The initial electrocardiogram showed inferolateral ST segment depression. The chest *x*-ray film was normal and haemoglobin was 16·1 g/dl. Nitroprusside therapy promptly returned the blood pressure to normal and her symptoms resolved. Analysis of urine by thin layer chromatography disclosed phenylpropanolamine and chlorpheniramine, and this was confirmed by gas chromatography-mass spectrophotometry. The total serum creatine kinase level and MB isoenzyme fraction were high at 12 hours and had returned to normal 36 hours after drug ingestion (Table). The electrocardiographic ST-T abnormalities persisted for 48 hours and then returned to normal. The subsequent course was uncomplicated and the blood pressure remained normal. Thyroid function tests, urinary metanephrine and vanillylmandelic acid levels, M-mode and two-dimensional echocardiograms, technetium pyrophosphate cardiac scintigraphic scan, and a submaximal graded exercise test were normal. Four months later the patient was asymptomatic and normotensive.

Table *Total serum creatine kinase (% MB fraction)**

	Admission	*12 hours*	*24 hours*	*36 to 48 hours*
Case 1	—	132 (2-5)	104 (11)	45 (<2)
Case 2	—	183 (6)	117 (2-5)	62 (<2)
Case 3	Normal	230 (2-5)	253 (<2)	67 (<2)

*Normals: creatine kinase 16-84 IU/l, MB fraction <2%.

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CASE 2

An agitated 13-year-old girl was admitted with headache two hours after the deliberate ingestion of eight capsules each containing phenylpropanolamine 50 mg, chlorpheniramine 8 mg, and isopropamide 2·5 mg. There was no history of hypertension or cardiovascular disease, or of other drug ingestion. Blood pressure was 190/110 mmHg and pulse rate 120. The respiratory and cardiovascular systems and the optic fundi were normal. Capsule fragments were obtained after induced vomiting. Over the next hour the diastolic blood pressure rose to 150 mmHg. Intravenous hydralazine (20 mg) returned the blood pressure to normal within one hour.

The electrocardiogram showed inferolateral ST segment depression (Fig. 1A) and ventricular bigeminy which resolved spontaneously (Fig. 1C).

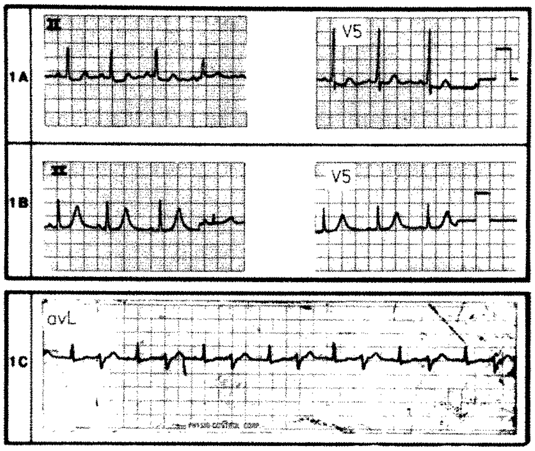

Fig. 1 *(A) Electrocardiogram (leads II and V5) from case 2 at the time of admission. There is depression of the ST segment in both leads. (B) Twenty-four hours later, the repolarisation abnormalities have resolved. (C) Electrocardiographic rhythm strip (lead aVL) from case 2 in the emergency room showing ventricular bigeminy.*

The chest x-ray film was normal. Analysis of urine showed phenylpropanolamine and chlorpheniramine. Total creatine kinase and the MB fraction were raised 12 and 24 hours after drug ingestion and subsequently returned to normal (Table). Quantitative chromatography confirmed the increase in the total creatine kinase and the MB isoenzyme. Electrocardiographic ST segment abnormalities resolved over 48 hours (Fig. 1B). Technetium pyrophosphate cardiac scintigraphy and M-mode and two-dimensional echocardiograms were normal. The subsequent course was uneventful and the patient was asymptomatic and normotensive two months after discharge.

CASE 3

A 31-year-old schizophrenic woman ingested approximately 40 tablets containing phenylpropanolamine 50 mg and caffeine 200 mg and began vomiting one hour later. There was no history of cardiovascular disease or hypertension. Medications included urecholine and trifluoperazine. The patient was agitated and the blood pressure was 180/120 mmHg, with a pulse rate of 90. Examination of the fundi, chest, and heart showed nothing abnormal. The chest x-ray film was normal, haemoglobin was 16·4 l/dl, and serum potassium 3·3 mmol/l. Analysis of urine disclosed phenylpropanolamine and caffeine.

The blood pressure returned to normal over three hours without treatment. The electrocardiogram was normal but an accelerated idioventricular rhythm developed (Fig. 2) for which lignocaine was given. Total creatine kinase and the MB fraction were normal on admission, raised 12 hours later, and had returned to normal at 36 hours (Table). No further rhythm disturbance was seen. M-mode and two-dimensional echocardiograms and technetium pyrophosphate scintigraphy were normal. One month after discharge the patient was normotensive and asymptomatic.

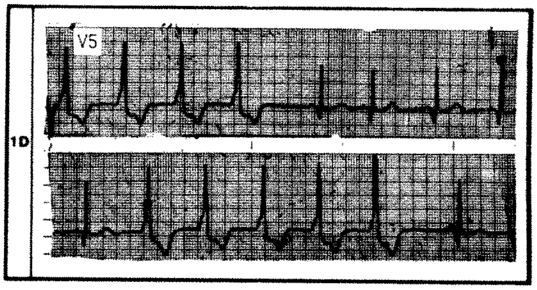

Fig. 2 *Electrocardiographic rhythm strip (modified lead V5) from case 3 on admission to the intensive care unit showing an accelerated idioventricular rhythm.*

Methods

Creatine kinase was determined using a modification of Rosalki's method[6] and its MB isoenzyme by electrophoresis. In case 2, determinations were also performed using quantitative chromatography on DEAE Sephadex A-50.[7]

Phenylpropanolamine was extracted from urine into an 80/20 mixture of chloroform/isopropyl alcohol and qualitatively assayed by gas chromatography-mass spectrophotometry. Phenylpropanolamine assay was also performed by thin layer chromatography.

Discussion

These cases illustrate that enzymatic and electrocardiographic evidence of myocardial injury may occur in young, healthy patients after phenylpropanolamine ingestion. Electrocardiographic repolarisation changes, ventricular arrhythmias, and clinical symptoms suggest that this myocardial injury may have important consequences, and each of our patients required monitoring in an intensive care unit. The initial patient, who had chest pain, high creatine kinase levels, and electrocardiographic abnormalities admitted taking only 50 mg of the drug. Though the patient was judged reliable, quantitative determination of phenylpropanolamine was not obtained. While it is thus possible that therapeutic doses of phenylpropanolamine have the potential for producing myocardial toxicity in certain patients, we cannot say this conclusively in our patient. The recognition of myocardial injury in two successive patients with intentional overdoses of phenylpropanolamine suggests, however, that this may be a common complication of excessive phenylpropanolamine ingestion.

Histological evidence of diffuse focal myocardial necrosis has been produced in animals by both sympathomimetic amines and catecholamines.[8 9] Infusions of noradrenaline or isoprenaline as brief as six hours can produce such lesions.[10] While the effects of phenylpropanolamine have not been studied, a variety of similar sympathomimetic amines have been shown to produce microscopical lesions of myocardial necrosis in rats.[5] Studies of patients with phaeochromocytoma have shown that prolonged excessive catecholamine stimulation is associated with similar myocardial lesions in humans,[11] and case reports of myocardial necrosis following infusions of noradrenaline given for only a few days suggest that such injury may also occur more acutely.[12]

These studies in both animals and humans indicate that excessive adrenergic stimulation can cause myocardial necrosis. Since phenylpropanolamine is a direct adrenergic agonist and also releases endogenous catecholamines, it is likely that it caused myocardial injury in our patients by this mechanism. Though there is a report of cardiomyopathy in a chronic amphetamine abuser,[13] were are not aware of previous reports of acute sympathomimetic ingestion resulting in either histological or clinical evidence of myocardial injury.

The way in which adrenergic stimulation could cause myocardial necrosis is unclear. Alpha-adrenergic mediated coronary vasoconstriction has been well documented in dogs,[14] but the ability of the pure beta-adrenergic agonist isoprenaline to produce myocardial necrosis[9] argues against this possibility. It is also unlikely that a primary increase in myocardial oxygen consumption secondary to hypertension and mild tachycardia resulted in myocardial ischaemia in our patients. Each was a young woman with no history of coronary artery disease or hypertension and no electrocardiographic or echocardiographic evidence of left ventricular hypertrophy. Histological studies of dogs given noradrenaline infusions to produce myocardial necrosis have shown increased platelet aggregates in myocardial capillaries. Pretreatment with antiplatelet agents reduces both the aggregates and the degree of myocardial necrosis.[15 16] Capillary occlusion by circulating platelet aggregates is thus a possible mechanism for myocardial injury.

While the formulations ingested by each of our patients contained additional drugs, the only agent common to all three patients was phenylpropanolamine. These additional drugs were pharmacologically dissimilar (chlorpheniramine, caffeine), and it is unlikely that they were the primary cause of myocardial injury. It is possible, however, that they contributed to the phenylpropanolamine toxicity. Caffeine increases plasma catecholamine levels[17] and chlorpheniramine inhibits neuronal reuptake of catecholamines.[18]

This report shows that clinical evidence of myocardial injury may result from the ingestion of excessive doses of phenylpropanolamine. While therapeutic doses may also cause such toxicity in certain subjects, this cannot be clearly established from our observations. Documentation of the incidence and relation of this adverse effect to drug dosage is needed because of the widespread availability of phenylpropanolamine.

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Initiation of ventricular fibrillation outside hospital in patients with acute ischaemic heart disease

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SUMMARY Factors which may predispose to ventricular fibrillation were assessed in 48 consecutive patients who developed ventricular fibrillation outside hospital after the arrival of a mobile coronary care team. Before the initiation of ventricular fibrillation, late cycle ventricular extrasystoles were recorded in 38 patients (79%) and R on T extrasystoles in 27 patients (56%). R on T extrasystoles were relatively infrequent—an average of three occurred during a mean monitoring time of 27 minutes. Multifocal extrasystoles occurred in only three patients (6%), consecutive extrasystoles in 14 (29%), and self-terminating ventricular tachycardia in three (6%). Ventricular extrasystoles occurring at more than five a minute were uncommon during this phase. The time from "warning arrhythmias" to the development of ventricular fibrillation in many patients was short, thus limiting the administration of antiarrhythmic agents. There was a significant increase in the heart rates recorded immediately before ventricular fibrillation when compared with those documented initially. Thus, an increase in heart rate appeared to be a predisposing factor in the initiation of ventricular fibrillation.

An R on T extrasystole was the most important factor in the initiation of ventricular fibrillation: it occurred in 33 patients (69%). In nine (19%) ventricular tachycardia and in six (12%) a late cycle extrasystole or idioventricular rhythm initiated ventricular fibrillation.

During the early minutes or hours after the onset of myocardial ischaemia or infarction, ventricular fibrillation is the major complication. The majority of patients are in ventricular fibrillation when first seen by prehospital units. Thus, it has been found[1] that among patients with primary ventricular fibrillation (fibrillation in the absence of pump failure or cardiogenic shock) during the first hour of myocardial infarction, 82% were in ventricular fibrillation before the mobile team arrived. Nevertheless, in order to assess factors that may initiate ventricular fibrillation, we decided to review the data on patients who developed it outside hospital after the arrival of the Belfast Mobile Coronary Care Unit.

Patients and methods

Between October 1972 and April 1977 we studied consecutively patients who developed ventricular fibrillation outside hospital. On arrival of the prehospital unit, the patient was immediately connected to an oscilloscope, and a two channel tape recorder. One channel allowed continuous recording of the electrocardiogram, the other, a speech channel, permitted the frequent documentation of blood pressure recordings by sphygmomanometer, and the time at which drugs were administered. A "Venflon" cannula was inserted into a forearm vein for the intravenous administration of drugs.

Treatment given by the family doctor, for example analgesics, atropine, or lignocaine, was recorded. We excluded from the study patients with ventricular fibrillation or sustained ventricular tachycardia when first seen.

Electrocardiographic monitoring was continuous during transport and for 10 minutes after the patient arrived in the hospital coronary care unit. Blood pressure was recorded on arrival with the patient, and at intervals before the patient was moved.

A permanent record of the electrocardiogram was obtained from tape recordings, and several specific heart rates were documented: (1) The heart rate when the patient was first seen and connected to the tape recorder (initial). (2) The heart rate immediately pre-

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ceding ventricular fibrillation (preventricular fibrillation). (3) The heart rate immediately before transfer in patients who developed ventricular fibrillation while being moved, or in the ambulance during the journey to hospital (premovement). The cardiac rhythm, frequency and type of extrasystoles, blood pressure, and therapeutic interventions were analysed from the tape recordings, and the results subjected to statistical analysis.

The diagnosis of myocardial infarction was made when at least two of the following were present: typical chest pain, clinically significant rise in cardiac enzymes, or characteristic evolving changes on the electrocardiogram. Myocardial infarction was also diagnosed at necropsy. An acute ischaemic episode was defined as prolonged chest pain at rest caused by acute myocardial ischaemia without evidence of infarction.

The prematurity index of ventricular premature beats was assessed by dividing the coupling interval of the ventricular premature beat (RR′) by the QT interval of the preceding normally conducted beat. A ventricular extrasystole with a prematurity index of <1 was considered to represent the R on T phenomenon, while a premature beat with an index of $\geqslant 1$ was termed long-coupling or late cycle.

Results

Fifty-two patients entered the study. Three patients were excluded because of malfunction of the recording apparatus and the record was unobtainable for analysis in a further patient. The study, therefore, was made up of 48 patients. Forty were men, aged 37 to 79 years (mean age 56 years), and eight were women aged 40 to 76 (mean age 59 years). The site of infarction was anterior in 29 (63%), inferior in 15 (33%), anterior and inferior in one, and subendocardial in one. One patient had myocardial ischaemia, and aortic stenosis was present in the remaining patient. Thirteen patients had had one or more previous myocardial infarctions. Thirty-nine patients had primary ventricular fibrillation and nine had secondary ventricular fibrillation.

The median time from onset of symptoms of myocardial infarction to arrival of the mobile coronary care unit was 68 minutes. Twenty-two patients were seen within one hour. The median time from onset of symptoms to development of ventricular fibrillation was 105 minutes. Ten patients developed ventricular fibrillation within one hour.

The electrocardiographic monitoring time before development of ventricular fibrillation varied from one to 80 minutes (mean 25 minutes).

Routine treatment before the acute incident consisted of beta-blocking agents in three patients, methyldopa in two, guanethidine in one, and glyceryl trinitrate in one patient. Before ventricular fibrillation, 37 patients received analgesics either from the family practitioner or from members of the mobile coronary care unit. Antiarrhythmic, vagolytic, and beta-sympatholytic agents administered intravenously and before ventricular fibrillation were atropine (eight), lignocaine (three), sotalol (two), atropine and practolol (atropine 0·6 mg, practolol 10 mg) (two), and atropine and sotalol (atropine 0·6 mg, sotalol 10 mg) (two). After the administration of atropine or beta-blocking agents no patient developed tachyarrhythmia with or without hypertension or bradyarrhythmia with or without hypotension.

On arrival of the mobile team, 25 patients were in sinus rhythm, 10 had sinus tachycardia, 10 had sinus bradycardia, two had atrial fibrillation, and one had second degree atrioventricular block. The blood pressure was recorded on arrival in 42 patients. In six patients it was not possible to take a blood pressure recording since the speed of development of ventricular fibrillation precluded the estimation of the blood pressure. The range of systolic pressures was 60 to 195 mmHg (mean 124 mmHg). The rhythm and blood pressure recorded immediately before the initiation of ventricular fibrillation showed that 27 patients were in sinus rhythm, 12 had sinus tachycardia, and two sinus bradycardia. Five had atrial fibrillation. Idioventricular rhythm was present in one and ventricular tachycardia in one. Both were self-terminating. Blood pressure was recorded in 41 of the 48 patients; the systolic blood pressure varied from 75 to 200 mmHg (mean 125 mmHg).

The range of the initial heart rates and those before ventricular fibrillation are recorded in Table 1. There was a significant increase in the heart rates immediately before ventricular fibrillation (paired t test of the differences between the initial and preventricular fibrillation heart rates, $p<0{\cdot}001$). On excluding those patients who had received atropine or a beta-blocking agent, the p value was still significant ($p<0{\cdot}01$). Fig. 1 shows the distribution of the initial and preventricular fibrillation heart rates. An increase in heart rate is shown for the majority of patients. In 12 of the 48 patients, ventricular fibrillation occurred during movement of the patient from the position when first seen (Table 2). There was a significant increase between the initial and premovement heart rates and

Table 1 *Initial and preventricular fibrillation heart rates in 48 patients*

Initial	47–175 (mean $84\pm4{\cdot}14$ SEM)/min
Pre-VF	52–214 (mean $98\pm4{\cdot}99$ SEM)/min

Paired t test $p<0{\cdot}001$.

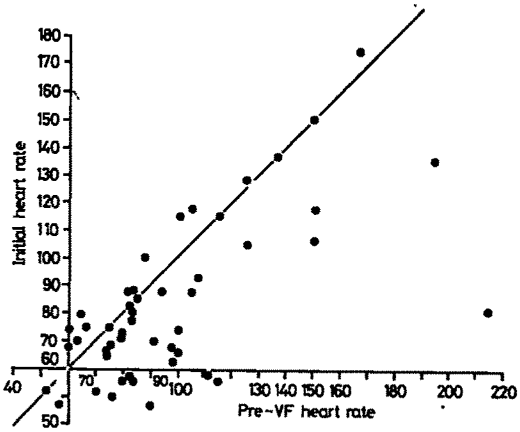

Fig. 1 *Initial and preventricular fibrillation heart rates in the 48 patients. The line drawn represents a heart rate of no change.*

between the initial and preventricular fibrillation heart rates.

Extrasystolic activity preceding ventricular fibrillation but excluding that initiating ventricular fibrillation was recorded (Table 3). Seventy-nine per cent had late cycle extrasystoles and 56% had R on T extrasystoles. Consecutive, multifocal, bigeminal ventricular extrasystoles, self-terminating ventricular tachycardia, and atrial extrasystoles were relatively infrequent. In six patients no ventricular extrasystoles were recorded. They had a shorter average monitoring time (nine minutes) than that of the whole group. The frequency distribution of late cycle ventricular extrasystoles in relation to the monitoring time is shown in Fig. 2. The average number of late cycle ventricular extrasystoles recorded was 13 for a mean monitoring time of 27 minutes. A similar graph (Fig. 3) plotted the frequency distribution of R on T extrasystoles and showed an average of three R on T extrasystoles for a mean monitoring time of 27 minutes.

Table 2 *Initial, premovement and preventricular fibrillation heart rates in 12 patients where ventricular fibrillation occurred during movement*

(A)	Initial heart rate	48–136 (mean 85±8·96 SEM)/min
(B)	Premovement heart rate	48–152 (mean 95·5±9·96 SEM)/min
(C)	Pre-VF heart rate	56–194 (mean 104±11·06 SEM/min

Paired t test between (A) and (B) 0·05>p>0·025.
Paired t test between (A) and (C) 0·02>p>0·01.

Table 3 *Extrasystoles recorded before initiation of ventricular fibrillation*

	No. of patients	*Incidence %*
Late cycle ventricular extrasystoles	38	79
R on T ventricular extrasystoles	27	56
Consecutive ventricular extrasystoles	14	29
Multifocal ventricular extrasystoles	3	6
Bigeminal ventricular extrasystoles	3	6
VT (self-terminating)	3	6
Atrial extrasystoles	3	6
No extrasystolic activity	6	12

Consecutive ventricular extrasystoles—two successive ventricular extrasystoles occurring in pairs. Bigeminal ventricular extrasystoles—a ventricular extrasystole alternating with a normally conducted beat for at least two normally conducted beats. VT (self-terminating) ventricular tachycardia—three or more successive ventricular extrasystoles at a ventricular rate of >120/minute and self-terminating.

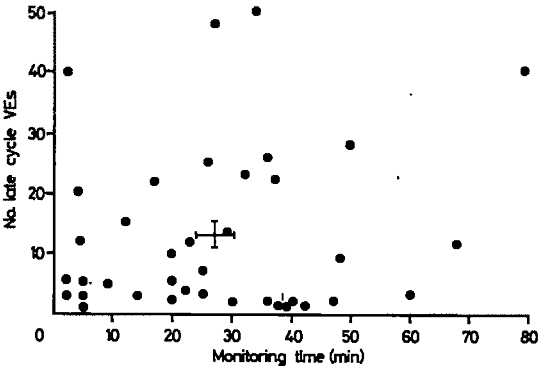

Fig. 2 *Frequency distribution of late cycle VEs (ventricular extrasystoles) (38 patients) in relation to monitoring time (mean 13 late cycle ventricular extrasystoles for average monitoring time of 27 minutes).*

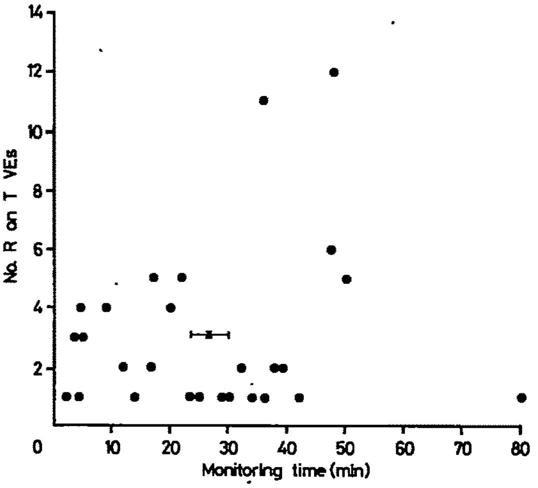

Fig. 3 *Frequency distribution of R on T extrasystoles (27 patients) in relation to monitoring time (mean three R on T extrasystoles for average monitoring time of 27 minutes).*

An R on T extrasystole initiated ventricular fibrillation in 33 of the 48 patients (Fig. 4). In three patients a late cycle ventricular extrasystole gave rise to ventricular fibrillation, idioventricular rhythm in a further three, and ventricular tachycardia in nine (Fig. 4).

Twenty-nine (60%) had an isolated episode of ventricular fibrillation and 19 (40%) had one or more episodes of ventricular fibrillation outside hospital after correction of the initial episode. Thirty-five (73%) patients survived to leave hospital.

Discussion

Sudden cardiac death is the leading cause of death among men aged 20 to 64 years.[2] Though ventricular fibrillation is the major cause of sudden death,[3-5] many aspects of sudden death still remain unsolved. Factors initiating ventricular fibrillation are largely unknown since this arrhythmia rarely develops in the community in the presence of continuous electrocardiographic monitoring.[6 7] Many sudden deaths are instantaneous and therefore do not allow time for electrocardiographic monitoring.

The significance of "warning" or premonitory arrhythmias which precede the development of ventricular fibrillation still gives rise to major debate. Generally accepted criteria for "warning arrhythmias" include ventricular extrasystoles falling into one of the four following categories: R on T, >5/minute, multifocal, coupled or in salvos.[8] In experimental and clinical studies R on T extrasystoles have been reported with varying frequency. A study in baboons showed that 69% who developed ventricular fibrillation within the first hour of acute myocardial infarction had R on T extrasystoles.[9] In one study it was found that of patients admitted within six hours of the onset of infarction, only 10% of those who developed primary ventricular fibrillation had R on T extrasystoles as "warning arrhythmias".[10] Of those with primary ventricular fibrillation, occurring in the majority within 24 hours of the onset of infarction, only 25% had antecedent R on T extrasystoles.[11] It is of interest that in these two studies[10 11] as many patients had R on T extrasystoles who went on to develop ventricular fibrillation as those who did not.

It may well be that the pattern or timing of ventricular extrasystoles as "warning arrhythmias" is not necessarily crucial to the development of ventricular fibrillation but the capacity of the infarcted ventricle to sustain repetitive beating.[12] In this study during the premonitory phase late cycle ventricular extrasys-

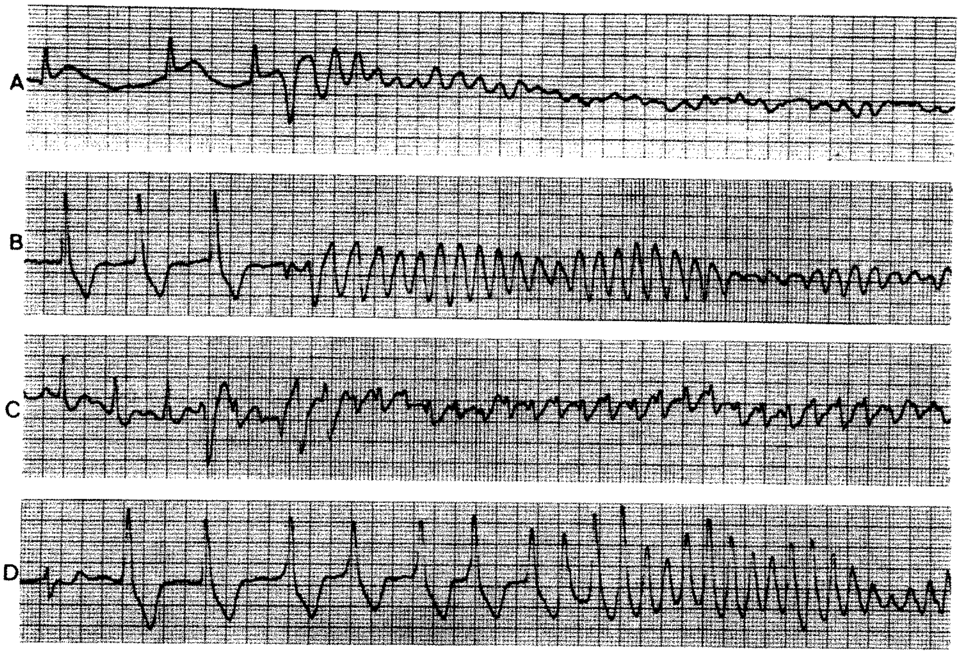

Fig. 4 *Initiation of ventricular fibrillation. (A) R on T extrasystole; (B) late cycle extrasystole; (C) ventricular tachycardia/ventricular flutter which degenerated into ventricular fibrillation; (D) idioventricular rhythm with rapid acceleration into ventricular fibrillation.*

toles were the most frequent, occurring in 38 (79%) patients. R on T ventricular extrasystoles were present in 27 (56%) patients. Only an average of three R on T extrasystoles were recorded, however, during a mean monitoring time of 27 minutes. Multifocal ventricular extrasystoles, consecutive or bigeminal extrasystoles were relatively infrequent. Ventricular extrasystoles occurring with a frequency of >5/minute were rare. In some patients a burst of ventricular extrasystoles immediately preceded the initiation of ventricular fibrillation (Fig. 5). Sustained ventricular tachycardia is rare during the early phase of acute myocardial infarction.[1,13] In this study, self-terminating ventricular tachycardia before the development of ventricular fibrillation occurred in three (6%) patients.

The time from the development of "warning arrhythmias" until ventricular fibrillation in many cases was very short and this precluded the institution of antiarrhythmic therapy. It therefore calls into question the significance of "warning arrhythmias" in the administration of antiarrhythmic therapy.

Major controversy still surrounds the initiation of ventricular fibrillation. Clinical significance of the vulnerable phase (R on T) was first emphasised by Smirk and Palmer.[14] In one study[15] an R on T extrasystole was the initiating event in 80% of those who developed primary ventricular fibrillation. In similar studies[10,11] the initiating event was an R on T extrasystole in 45% and 50%, respectively. Clinical tests and experimental work have shown that ventricular fibrillation may be initiated by an R on T or a late cycle extrasystole.[12,16] In our study an R on T extrasystole was the most important factor in the initiation of ventricular fibrillation: it was found in 69% of the patients. A late cycle ventricular extrasystole or idioventricular rhythm rarely initiated ventricular fibrillation. Ventricular fibrillation was initiated by ventricular tachycardia in 19% of patients. In a study[7] of seven patients with coronary artery disease who died suddenly during ambulatory monitoring, ventricular tachycardia degenerated into ventricular fibrillation in all seven.

Clinical and experimental studies have shown that ventricular fibrillation may be associated with extremes of heart rate, bradycardia, and tachycardia.[1,17,18] Sympathetic overactivity most frequently associated with anterior infarction was present in 35% of patients seen within 30 minutes of the onset of symptoms.[1] During the movement of patients with acute myocardial infarction, and despite analgesia, a heart rate of ≥100/minute has been recorded in 45%.[19] Increased plasma catecholamine levels have been reported in animals after left anterior descending coronary artery occlusion and in man during the first hour of acute myocardial infarction.[20] Sympathetic overactivity in association with acute myocardial infarction may cause a fall in ventricular fibrillation

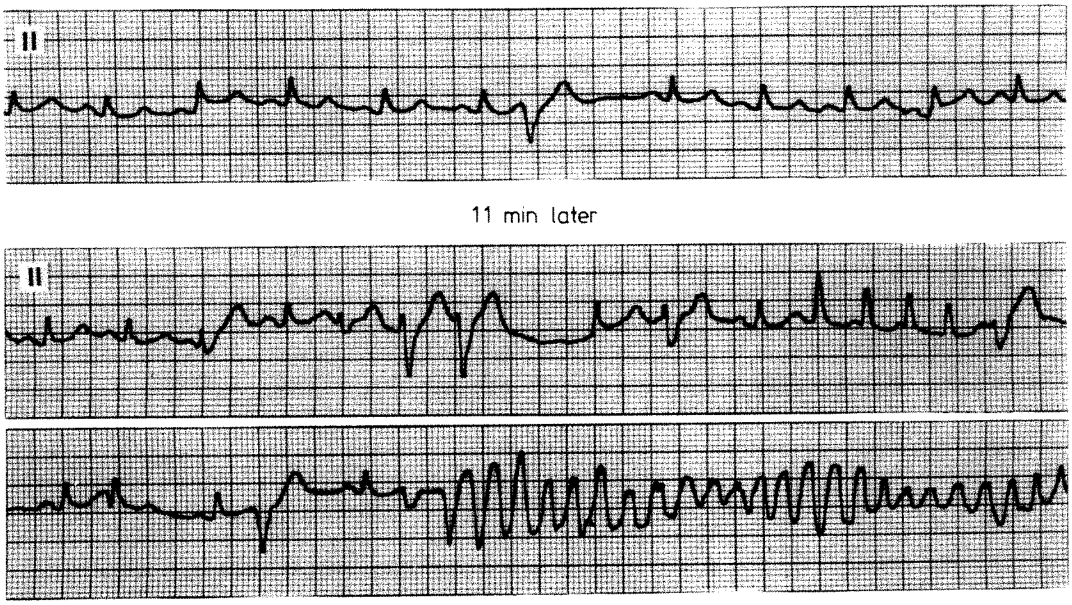

Fig. 5 *Top tracing—single R on T extrasystole during out-of-hospital monitoring, heart rate less than 100/minute (lead II ECG). Eleven minutes after top tracing, heart rate increased, burst of late cycle and R on T extrasystoles ending in ventricular fibrillation (second and third tracings continuous).*

threshold,[21] and since heart rate is a major determinant of myocardial oxygen demand, an increase in the extent of myocardial ischaemic injury. When beta-blockers are administered in the experimental situation, the incidence of ventricular fibrillation is reduced.[22 23] In this study the heart rhythm immediately preceding the initiation of ventricular fibrillation did not differ significantly from that reported when the patient was seen initially, but there was a significant increase in the heart rate from the time the patient was first seen until that recorded immediately before ventricular fibrillation. This was so even after excluding patients who had received prior treatment with atropine or beta-blocking agents. When ventricular fibrillation occurred during the movement of a patient to hospital there was also a significant increase in heart rate from that recorded initially.

In a study of long and short term survivors from out-of-hospital ventricular fibrillation[5] it was found that acute myocardial infarction was present in only 39%, and ischaemia without infarction in 34%. In long term survivors of out-of-hospital ventricular fibrillation, myocardial necrosis based on electrocardiographic or enzyme studies was present in 49·5%, and only 17% had an acute transmural infarction.[4] In 50·5% of their patients there was no evidence of myocardial necrosis. Of the group in ventricular fibrillation when the Seattle unit arrived, myocardial necrosis was present in 42% and only 10% showed acute transmural infarction. In contrast with those who developed ventricular fibrillation after arrival of the unit, 79% had evidence of myocardial necrosis, and 50% showed acute transmural infarction. In our study where ventricular fibrillation occurred after the arrival of the unit, 96% of short and long term survivors had an acute myocardial infarction. The minimum time from onset of symptoms to the development of ventricular fibrillation was 32 minutes. No patient suffered instantaneous death. It is impossible to say, therefore, that the factors leading to ventricular fibrillation in this group of patients would be identical in those who die instantaneously.

In this study more patients had an anterior than a diaphragmatic infarction. In two studies[11 15] anterior infarctions dominated and in another study[5] lesions of the anterior wall dominated, yet in one report[24] there was a predominance of inferior infarctions. In an earlier study from Belfast, of ventricular fibrillation outside hospital, there was an equal incidence of anterior and inferior infarctions.[3]

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Missing coronary artery
Review of technical problems in coronary arteriography resulting from anatomical variants

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SUMMARY In 75 (0·9%) of 8235 patients without associated congenital heart disease studied by arteriography, a vessel was missing from its normal location, and this was the result of an anomalous origin. Symptoms attributable to these aberrant vessels were present in 19 of the 75 patients. Though rare, these anomalies can produce specific clinicopathological entities which can be diagnosed angiographically and treated surgically. Failure to recognise these anomalies of coronary anatomy prolonged arteriographic procedures and led to repeated catheterisations in 28 of the 75 cases (37%).

Coronary arteriography is routinely used as a diagnostic measure or as a prelude to surgical treatment. Failure to visualise a coronary artery division is relatively frequent and generally attributable to a complete proximal occlusion, even if no stump of blocked artery is demonstrated. Failure to intubate a coronary artery is usually the result of inadequate technique. Both of these failures may be caused by congenital variants of anatomy with which the investigator should be familiar.

In this paper we survey and illustrate the congenital variations of the coronary arteries which were documented in 75 out of 8235 patients without associated congenital heart disease, discuss their incidence in the routine investigation of patients with suspected ischaemic heart disease, and suggest a methodical approach to their recognition.

Patients and methods

Major anatomical variations of the coronary circulation were documented in 75 of 8235 patients (0·9%) who underwent coronary arteriography for suspicion or exclusion of coronary artery disease at the National Heart and Chest Hospitals and The Middlesex Hospital over a seven year period ending December 1980. Patients' data are shown in Table 1; those with associated congenital heart disease were excluded.

Their ages were 16 to 66 years (mean 44) at the time of angiography; 51 were male and 24 female. Symptoms attributable to the aberrant vessel were present in 19 of the 75 (25%). Sixteen patients had angina, eight of them with dyspnoea on exertion; in addition two presented with episodes of palpitation caused by ventricular tachyarrhythmias and one further patient was investigated because of unexplained episodes of exertional dyspnoea and syncope. The aberrant origin and course of the coronary arteries was diagnosed by angiography alone in 63 patients. A clinical diagnosis

Table 1 *Patient data (75 patients out of 8235 undergoing coronary angiography)*

Symptoms attributable to aberrant vessel	
Angina	8
Angina and dyspnoea	8
Palpitation	2
Unexplained exertional dyspnoea and syncope	1
Anomalies leading to symptoms	
Left anterior descending from pulmonary artery	2
Left coronary artery from anterior sinus	3
Left coronary artery from pulmonary artery	10
Stenosis in aberrant vessel	4
Electrocardiogram	
Ischaemic ST-T changes	28
Infarction (Q waves)	15
Normal	32
Associated findings at catheterisation	
Atherosclerotic occlusive disease	33
(Stenosis in aberrant vessel	8)
Valvular disease	12
Akinetic or aneurysmal wall motion	12
Congenital absence of left pericardium	1
Coarctation	1
No evidence of heart disease	16

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of anomalous origin of the left coronary artery from the pulmonary artery was made in the remaining 12 patients who presented in adult life with the classical features of this anomaly. Electrocardiography suggested myocardial ischaemia in 28 patients and transmural myocardial infarction in 15; in 10 of the latter the necrosis was caused by the retrograde flow in the left coronary artery.

Investigations showed no other evidence of heart disease in 16 patients, atherosclerotic coronary occlusive disease in 33, and valvular heart disease in 12 (congenital bicuspid aortic valve in three, rheumatic carditis in nine). Twelve additional patients had angiographic evidence of infarction (akinetic or aneurysmal wall motion) and two more had associated congenital abnormalities (coarctation of the aorta and congenital absence of the left pericardium). Coronary arteriography was performed in all cases using either the Sones or the Judkins technique. In 28 of the 75 cases (37%) the procedure was repeated because of inadequate visualisation of the aberrant vessel. Fifteen patients were reinvestigated once, nine twice, three three times, and one on four occasions before a correct diagnosis could be made.

Arteriographic findings

The apparently missing coronary artery at arteriography could be analysed under four groups (Table 2).

(1) MISSING ANTERIOR DESCENDING CORONARY ARTERY

Failure to visualise the anterior descending branch of the left coronary artery in the normal location usually occurred when the anterior descending and circumflex divisions had independent aortic origins in the left sinus of Valsalva, an anomaly encountered in eight patients.

More rarely the anterior descending coronary artery emerged from the right sinus of Valsalva, either independently or jointly with the right coronary artery (Fig. 1); this variant was found in four patients.

Finally, in two patients the anterior descending coronary artery originated from the pulmonary artery. The angiographic appearances were characteristic, the left main stem leading directly to a dilated circumflex division only and after a short delay, and a very large vessel in the position of the anterior descending opacifying, from which contrast streamed into the main pulmonary artery (Fig. 2). This aberrant

Table 2 *Angiographic findings*

Variants of coronary anatomy	*No. of patients*
(1) *Missing left anterior descending (LAD)*	
(a) Separate origin LAD and LCx in left sinus of Valsalva	8
(b) Origin LAD from right sinus of Valsalva or from RCA	4
(c) LAD from PA	2
(2) *Missing left circumflex artery (LCx)*	
(a) Separate origin LAD and LCx in left sinus of Valsalva (as 1a)	8
(b) Origin LCx from right sinus of Valsalva or RCA	26
(3) *Missing right coronary artery (RCA)*	
(a) RCA and LCA from left sinus of Valsalva (2) RCA from LCA (1) Extreme left dominance (4)	7
(b) Separate origin RCA and long conus artery	12
(4) *Missing left coronary artery (LCA)*	
(a) LCA from right sinus of Valsalva	2
(b) LCA from RCA	1
(c) LCA from PA	13

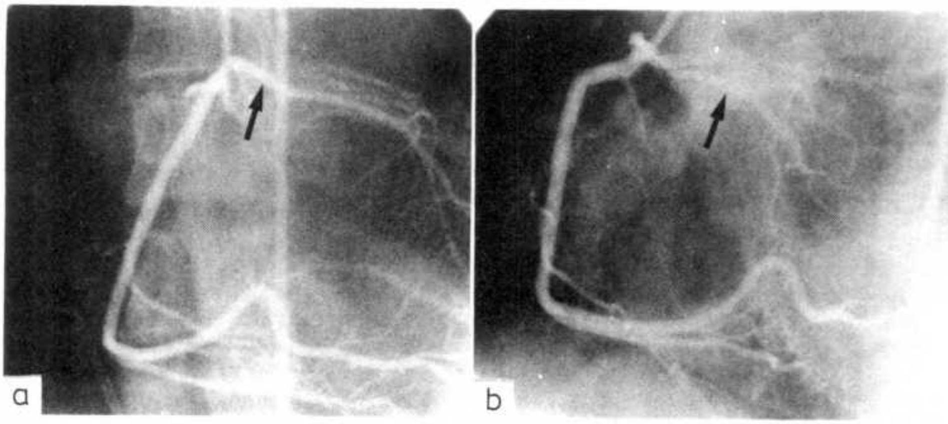

Fig. 1 *Origin of the left anterior descending from the right sinus of Valsalva (joint ostium with right coronary artery). (a) Anteroposterior view; (b) left anterior oblique projection. Arrow indicates the aberrant left anterior descending coronary artery.*

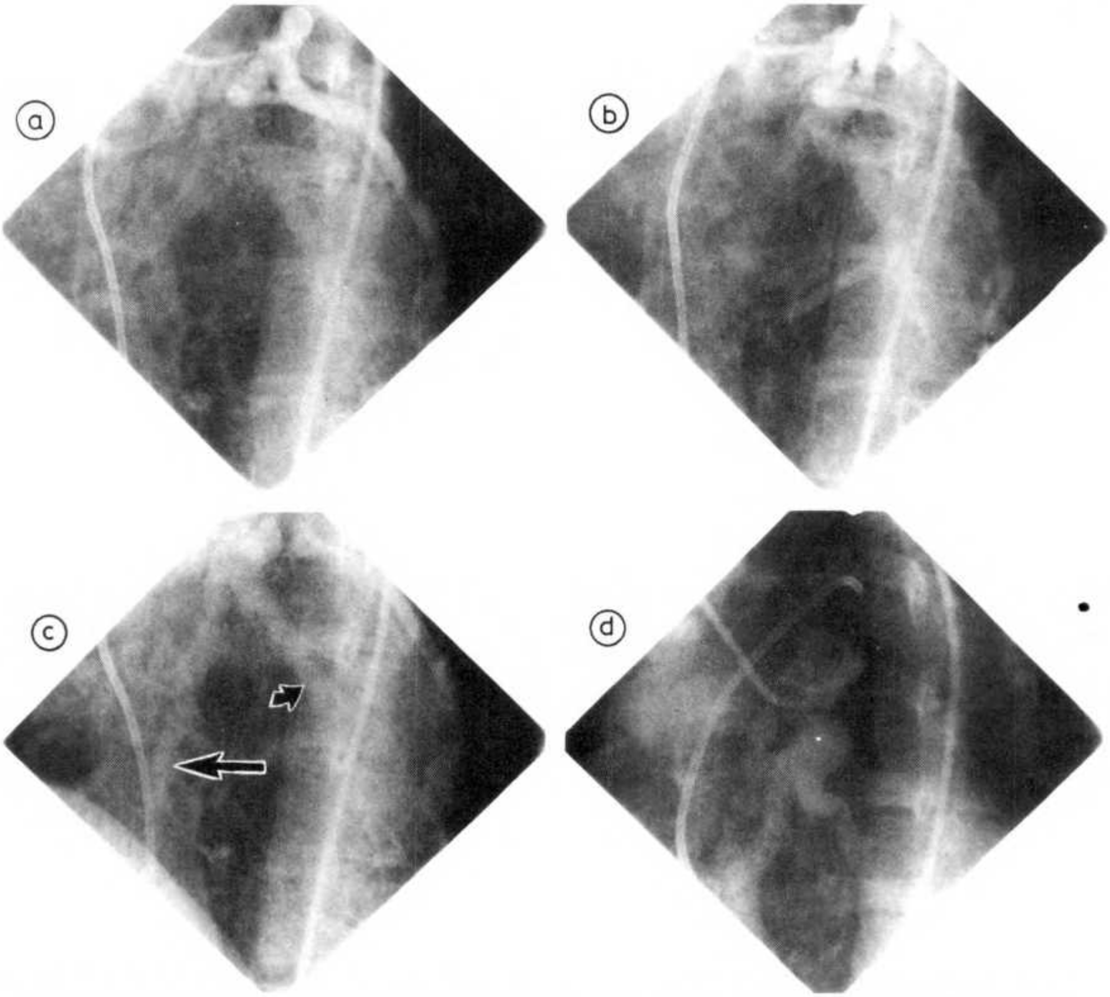

Fig. 2 *Abnormal origin of the left anterior descending coronary artery from the pulmonary artery. (a) and (b) Left coronary injection, left anterior oblique projection. Early arterial phase, showing a large circumflex coronary artery. Note the left anterior descending coronary artery fails to opacify. (c) Late phase, showing delayed filling of the dilated left anterior descending coronary artery (large arrow) and diagonal (small arrow) through collaterals. (d) Contrast medium streaming into the main pulmonary artery.*

anterior descending vessel also filled when the right coronary artery was injected

(2) MISSING LEFT CIRCUMFLEX ARTERY

The commonest variant leading to an apparent absence of the circumflex was when this vessel originated from the right coronary artery either as a branch of the latter or independently from a separate ostium in the right coronary sinus (Fig. 3 and 4). This variation was present in 26 of the 75 patients (35%). The abnormal circumflex usually travelled around the back of the aorta to the left atrioventricular groove and then pursued its normal course over the free wall of the left ventricle. Apparent absence of the left circumflex artery was also noted in the eight patients with separate origins of the anterior descending and circumflex arteries in the left sinus of Valsalva.

(3) MISSING RIGHT CORONARY ARTERY

In seven cases no right coronary ostium or artery was present. In two of these the ostium originated from the left coronary sinus (Fig. 5) and in a third the right coronary was a proximal branch of the left. In these cases the right coronary travelled to the right and anteriorly, between the aorta and right ventricular infundibulum, to reach its usual anatomical location.

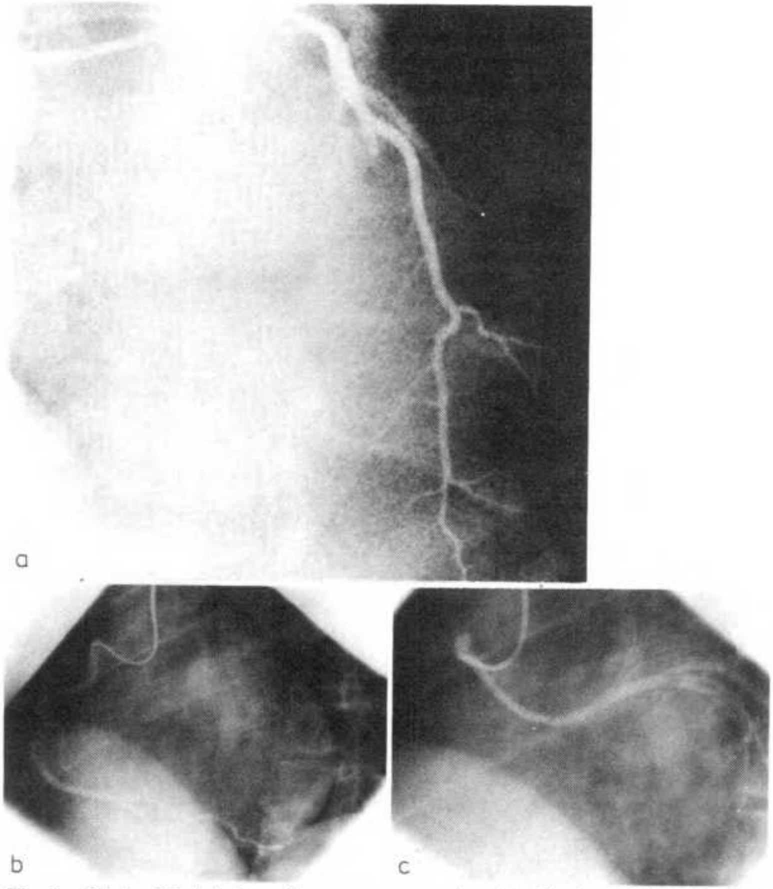

Fig. 3 *Origin of the left circumflex coronary artery from the right sinus of Valsalva. Left anterior oblique projection. (a) Only an isolated left anterior coronary descending artery fills from the left sinus of Valsalva. (b) Selective injection of right coronary artery in right sinus of Valsalva. (c) Selective opacification of left circumflex from separate ostium in right sinus of Valsalva.*

In the other four patients the right coronary artery was entirely replaced by a large circumflex which continued round the heart to reach the right atrioventricular groove to supply the right ventricular branches (extreme left dominance) (Fig. 6).

A right ventricular branch or the conus artery may be selectively catheterised either as a proximal branch of the right coronary or when either of these have an independent ostium (Fig. 7). There were 12 patients who had a separate origin of a long, low branching conus artery which followed an anterior course in front of the right ventricular outflow tract to reach the lateral surface of the heart.

(4) MISSING LEFT CORONARY ARTERY

There were three patients in whom the left coronary artery originated in the right aortic sinus (Fig. 8); one of these had a common ostium for both the left and right coronary arteries. From this abnormal ostium, the left main coronary artery then curved to the left and posteriorly, running intramurally inside the aortic wall, between the aorta and the right ventricular infundibulum to reach the left coronary sinus. From that point onwards the left coronary artery had a normal course and distribution behind the pulmonary artery. These patients all had ischaemic symptoms though their coronary arteries were free of atheroma.

In 13 cases the left coronary artery was a branch of the pulmonary artery. The right coronary artery filled from the aorta and was grossly dilated; after a shorter delay, the left coronary artery opacified via extensive collaterals and the contrast was seen streaming into the main pulmonary artery. Selective right coronary arteriography indicated associated stenosis in two

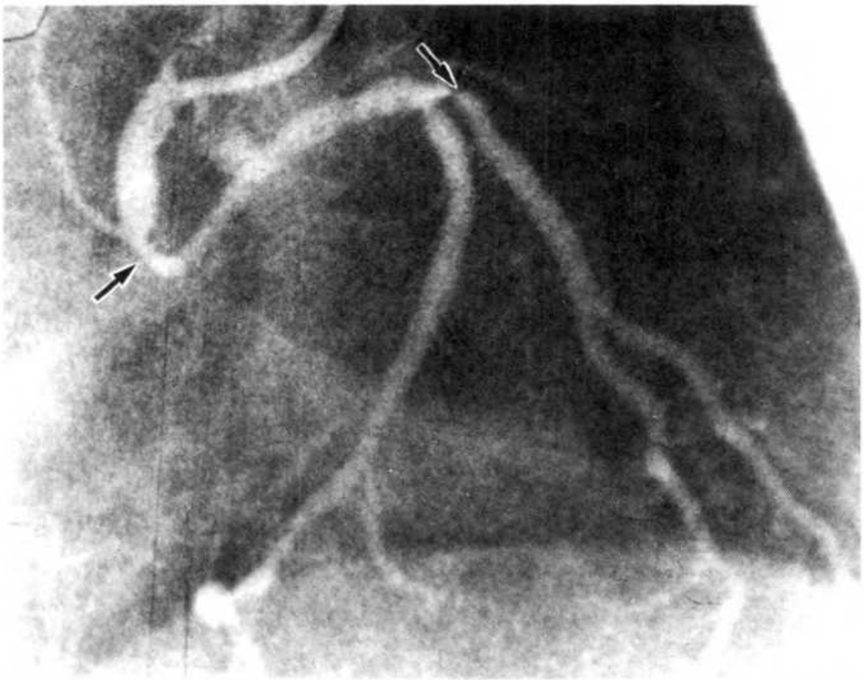

Fig. 4 *Abnormal origin of the left circumflex from the right sinus of Valsalva. The aberrant vessel has significant atherosclerotic narrowing (arrows).*

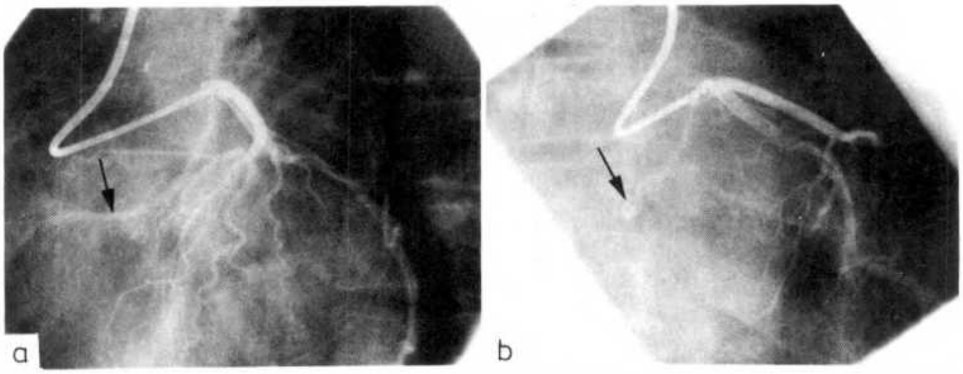

Fig. 5 *Origin of the right coronary artery from the left sinus of Valsalva, jointly with the left coronary artery. (a) Left anterior oblique and (b) right anterior oblique projection. The aberrant right coronary artery is arrowed.*

patients with this anomaly who had undergone previous surgical attempted ligation of the aberrant vessel.

Surgery

Surgical confirmation of the angiographic diagnosis was obtained in 41 patients; 14 of these underwent surgery for an anomalous vessel which produced significant abnormalities of myocardial perfusion, with relief of the presenting symptoms. These patients can be divided into three major groups: (1) two had the anterior descending branch of the left coronary artery arising from the pulmonary artery treated by ligation and vein grafting; (2) two had the left coronary artery arising from the anterior sinus and both underwent successful anatomical correction; (3) ten had the left coronary artery arising from the pulmonary artery, all with reversal of flow and left to

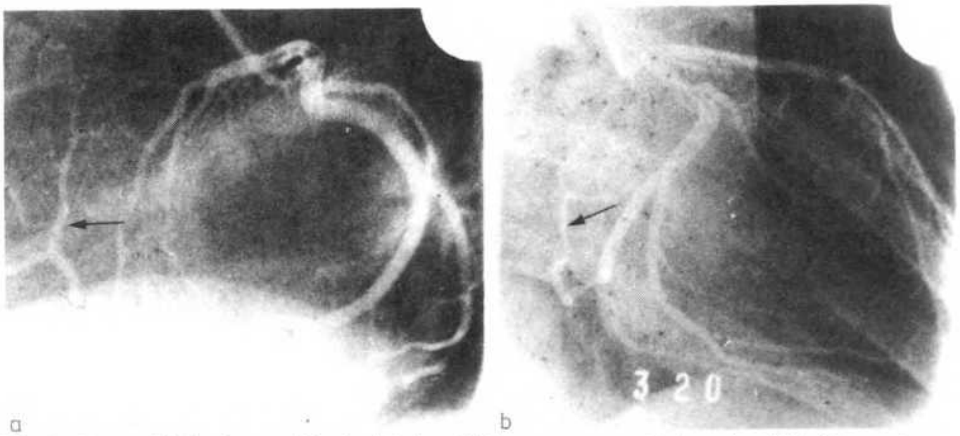

Fig. 6 *Extreme left dominance. Selective injection of left coronary artery. (a) Lateral and (b) right anterior oblique projection. The left circumflex continues around the heart in the right atrioventricular groove to replace the right coronary artery (arrowed).*

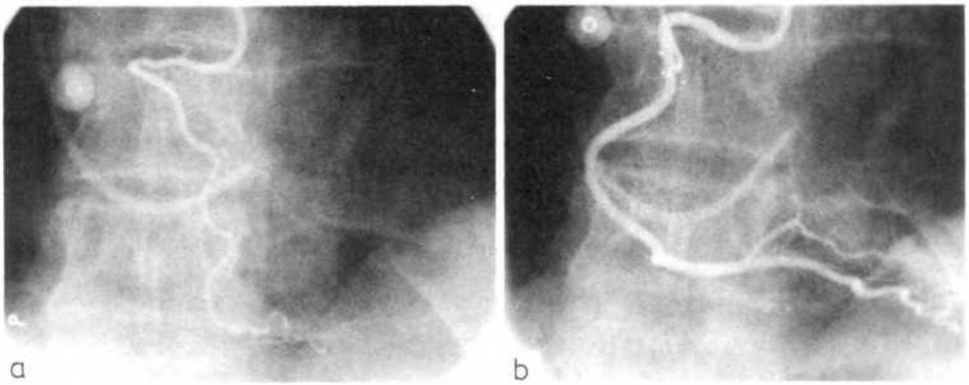

Fig. 7 *Separate origin of the right coronary artery and long right ventricular branch. (a) Selective right ventricular branch injection; (b) the main right coronary artery is opacified.*

right shunting; anatomical correction was performed in five and other methods of revascularisation with either vein grafts or an antologous left subclavian artery segment were used in the other five patients.

A further five patients underwent coronary surgery for narrowing or occlusion of a major aberrant vessel.

Discussion

The demonstration of anatomical changes in the coronary arteries has become important in patient management but visualisation of all coronary arteries is not always achieved. This, however, is usually because of imperfect technique. In a small proportion of patients one or more arteries have an atypical origin and these morphological variants may lead to difficulties in the performance or interpretation of the coronary arteriograms. It is possible that these aberrant vessels are not as rare as published reviews suggest.[1-3] As most of them are not associated with physiological upset, they show no typical clinical picture and are detected only by careful arteriographic technique. The incidence in our series was only 0·9%, but in this retrospective study cases were included only if the anomalous vessel was adequately filled on the arteriogram. In many cases with suspected aberrant vessels the examination was inadequate and these patients were excluded from further analysis.

It has become increasingly evident that some of these aberrant vessels can be associated with a variety of syndromes, from angina pectoris to sudden death.[4-7] Symptoms predominantly of exertional angina and attributable to the aberrant vessel were present in 19 (25%) of the 75 cases in our series (0·2% of the whole). A further 33 (44%) of the 75 patients had angina attributable to significant coronary artery

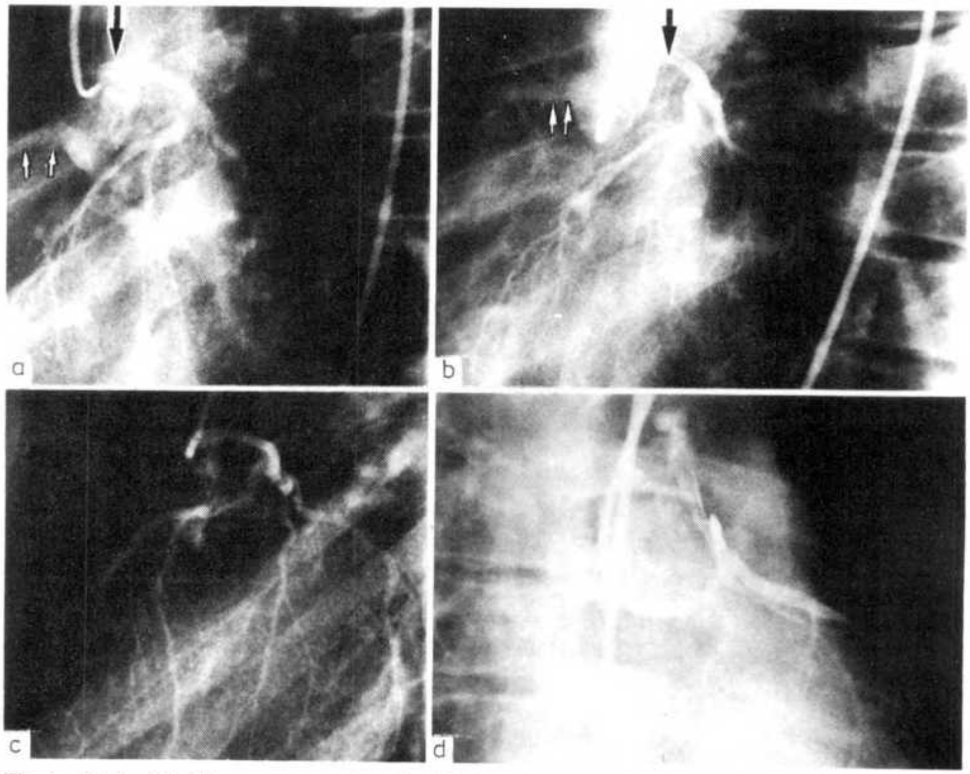

Fig. 8 *Origin of the left coronary artery from the right sinus of Valsalva. Selective left coronary injection. (a) and (b) Left anterior oblique views. The normal right coronary ostium (small arrows) is seen in profile. The ostium of the left coronary artery is clearly anterior (large arrows). (c) Lateral view. Note the posterior course of the left main stem which when normal appears end-on in this view. (d) Right anterior oblique view. Catheter filling the left coronary artery is lying in the anterior sinus of Valsalva.*

disease; of these, eight had narrowing or occlusion in the aberrant vessel (Fig. 4).

Failure to visualise a coronary artery should alert the operator to the possibility of an aberrant vessel, as coronary arteries rarely disappear when diseased and a blocked vessel almost invariably fills distally by collateral flow, except in the presence of aneurysm.[8] The first problem is to recognise that opacification is incomplete and most difficulty occurs with the branches of the left coronary artery. It is important to check that the left coronary artery gives both anterior descending and circumflex branches before accepting that opacification is complete. The true lateral view is important where there is doubt.[9]

(1) ABSENT LEFT CORONARY BRANCHES

If only the anterior descending fills when the catheter enters an artery in the left sinus of Valsalva, the most frequent origin of the circumflex is either as a proximal branch of the right coronary artery or from a separate ostium in the right sinus of Valsalva (Fig. 3) and this area should be explored. If, however, the catheter enters only the circumflex from the left sinus of Valsalva the most likely site of origin of the anterior descending is from the same (left) sinus and its ostium is usually near to that of the circumflex. Only rarely does the anterior descending originate from the right coronary artery or right sinus of Valsalva (Fig. 1). These anatomical variants can lead to technically difficult studies but they generally have little importance in the absence of atherosclerotic narrowing in the aberrant vessel.[10] When the abnormal circumflex originates from the right sinus of Valsalva, however, and follows a retroaortic course, it may inadvertently be damaged during mitral valve surgery,[11] with consequent myocardial infarction.

With a short left main stem the catheter may go selectively into one or other division; this should be apparent if the contrast is injected fast enough to reflux into the sinus of Valsalva, when both branches will be visualised.

In two patients who presented with angina in adult life the anterior descending originated from the pulmonary artery (Fig. 2). The diagnosis could easily be missed as the demonstration of two coronary ostia arising from the aorta, with very large and tortuous arteries, may suggest a form of coronary fistula, rather than the possibility of an anomalous artery with a third ostium in the pulmonary trunk. This anomaly, though rare, is important as symptoms may be relieved by ligation or grafting of the aberrant vessel.[12]

(2) ABSENT RIGHT CORONARY ARTERY

Although difficulty in intubating the right coronary artery is not rare, probing the right sinus of Valsalva with test injections will usually succeed in locating the ostium. If this fails, the investigator should review the appearances of the left coronary artery to check that the right is not a branch of the left, either proximal (from the main stem or left coronary sinus) or terminal (Fig. 5 and 6). This condition, though of morphological interest, appears to have a fairly benign clinical course.[13]

The origin of the right coronary artery from the pulmonary artery is rare and relatively benign,[14] and we did not encounter this anomaly.

The conus branch of the right coronary artery can be a source of technical difficulty during attempts to visualise the right coronary artery if the catheter goes selectively into it. The investigator must be alert to this possibility by keeping in mind the relative balance between the circumflex and the right coronary arteries. The clinical importance of this lies in the fact that the main right coronary may not be opacified and contrast injection into the conus branch may precipitate arrhythmias. Furthermore, the conus branch may be a major source of collateral circulation in the presence of occlusive disease.[15]

(3) ABSENT LEFT CORONARY ARTERY

Even in adult patients, the commonest reason for failing to find the ostium of the left main coronary artery in its usual site in the left sinus of Valsalva was when it arose from the pulmonary artery (13 of the 16 cases). This did not present a problem as in the majority the diagnosis was obvious clinically. The origin of the left coronary artery from the pulmonary artery is rare but of great physiological and clinical importance since it produces symptoms, is diagnosable during life, and is surgically treatable.[16–18] The few patients who survive infancy and later in life present with angina and evidence of ischaemia but no signs of necrosis of the left ventricle have a better prognosis than those showing the classical clinical picture.[19]

In the remaining three patients in whom the left coronary ostium was not in its normal position, the left coronary artery originated from the right (anterior) aortic sinus (jointly with the right coronary artery in one case), just in front of the intercoronary commissure (Fig. 8). This sinus should therefore be carefully explored when there is difficulty in finding the left coronary artery in its normal location, as this anomalous origin may cause symptoms resulting from myocardial ischaemia and may even lead to sudden death at a young age.[20–23] In most of the patients reported there has been a history of exertional angina or syncope (as in the three patients in our series), together with anatomical or functional obstruction of this aberrant left coronary, most probably caused by acute angulation of the ostium and compression of the intramural segment. Because of the grave prognosis, coronary surgery should be considered in young symptomatic patients with this anomalous origin of the left coronary artery.[13 24]

That a coronary artery is apparently missing is of considerable importance to both patient and investigator. Some anomalies may produce specific clinicopathological entities; equally as important, failure to recognise them may lead to inadequate and prolonged procedures. In 38% of our patients with coronary anomalies catheterisation had to be repeated, in one patient four times, to elucidate the problem before a correct diagnosis and curative surgery could be performed. Similarly, several patients had protracted catheterisation for apparent failure to intubate arteries which had already been opacified in an unexpected way.

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Isolated disease of left anterior descending coronary artery

Angiocardiographic and clinical study of 218 patients

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SUMMARY The angiocardiographic and clinical findings in 218 patients with significant obstruction confined to the left anterior descending coronary artery were reviewed to study the influence of the site of obstruction and of the collateral circulation on clinical presentation and prognosis. One hundred and fifty-six patients had been managed medically, 51 had had aortocoronary bypass operations, and 11 had had left ventricular aneurysms excised.

The artery was divided into three segments: left anterior descending 1 (LAD1) from its origin to the first septal branch, left anterior descending 2 (LAD2) from the first septal to the first diagonal branch, and left anterior descending 3 (LAD3) the remaining distal vessel.

Cardiogenic shock occurred only in patients with LAD1 lesions, but apart from this the clinical presentation bore no consistent relation to the site of disease. Patients with proximal lesions were more likely to have a "positive" exercise test, had more severely impaired left ventricular function, and had a worse prognosis than those with more distal disease. Non-visualisation of collateral vessels in patients with left anterior descending occlusion was associated with extensive infarction, and patients who presented with infarction had more severely impaired ventricular function than those who presented with angina and subsequently had an infarction. Left ventricular function was poor at the time of angiography in 11 of 12 of those who subsequently died; it is therefore unlikely that the prognosis of patients with isolated left anterior descending obstruction could be improved by expanding the indication for aortocoronary bypass from that of severe angina.

The notion that a proximal obstruction in a coronary artery is more dangerous than an obstruction distal to one or more of its major branches is logical, but difficult to prove because of other factors influencing the outcome in an individual patient. With the exception of left main stem lesions, the emphasis of much diagnostic activity in recent years has been directed to the assessment of patients according to the number of diseased vessels and the severity of obstruction rather than its site. "Significant" obstruction confined to one coronary artery is a common angiographic finding[1-4] which provides an opportunity to study the influence of arteriosclerotic lesions at different levels in the coronary artery tree. Because of their numerical preponderance[2-4] and a less certain prognosis in comparison with others with "single vessel disease"[3 5 6] we have examined a group of patients with greater than 50% reduction in diameter confined to the left anterior descending artery.

Patients and methods

Since 1971, clinical information and details of coronary arteriograms carried out on patients investigated at the London Chest Hospital have been recorded on mark-sense cards and stored in a computer. From this we have retrieved details of all patients with greater than 50% reduction in diameter of the left anterior descending artery (including those with additional diagonal branch disease), but with the left circumflex and right coronary arteries and their branches, and the left main stem, normal or stenosed by less than

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50%. Patients living outside the United Kingdom were excluded. The final study group comprised 218 patients, 180 men and 38 women, aged 27 to 71 (mean 50) years.

Angina was graded on a scale of 1 to 4, grade 1 being angina occurring only with severe exertion, grade 2 during normal activities, grade 3 with minimal exertion, and grade 4 at rest (with or without additional effort angina). The electrocardiogram was regarded as showing evidence of previous infarction if there were pathological Q waves, or a progressive reduction in R wave amplitude in the chest leads ("poor R wave progression"). A history of infarction was accepted even in the absence of these electrocardiographic changes at the time of investigation. For patients not followed up by ourselves information was obtained whenever possible from the family doctor or referring physician. All were "tagged" with the Registrar of Births and Deaths, so that follow-up with respect to mortality is complete to January 1980, unless death occurred outside the United Kingdom.

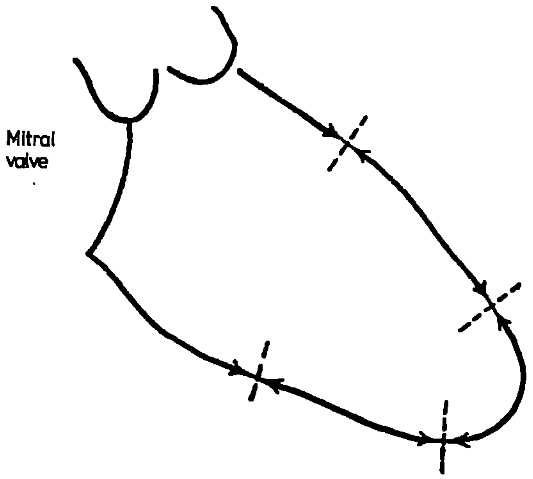

Fig. 1 *Diagram of left ventriculogram in 30° right anterior oblique projection showing division of the wall into five segments.*

ANGIOGRAPHIC ANALYSIS

The left coronary artery injections were made in posteroanterior, right anterior oblique 30°, and left anterior oblique 60° projections, and the right coronary in at least two of these. The anterior descending artery from its origin to the first septal branch was designated LAD1, from the first septal to the first diagonal branch LAD2, and the remainder of the distal vessel LAD3. In six patients the diagonal branch was proximal to the first septal branch and in these LAD1 was taken to the origin of the diagonal, and LAD2 from the diagonal to the first septal. In some patients the left main stem divided into three vessels: the main circumflex, the anterior descending, and a "trifurcation" vessel. In four patients this "trifurcation" branch supplied the anterolateral wall of the left ventricle (that is diagonal territory), and the anterior descending artery was considered to have only two segments, LAD2 and LAD3, whose junction was the first septal branch. Four patients with both LAD3 and diagonal lesions were classified as having LAD2 disease. The extent of reduction of diameter in each segment was measured. In making subsequent comparisons between patients with disease in different sites, those with multiple left anterior descending lesions were classified according to the most proximal obstruction of greater than 50%. The presence or absence of collateral channels, and whether or not the artery distal to an occlusion was seen, were also recorded.

The left ventricle was assessed from the 30° right anterior oblique ventriculogram. Ejection fraction was determined using a planimeter; ectopic and post-ectopic beats were not analysed. The outline of the ventricle was divided into the five segments illustrated in Fig. 1[7] and each was designated as showing normal contraction, hypokinesia, akinesia, or dyskinesia in systole.

STATISTICAL ANALYSIS

Means and proportions were compared by calculation of the standard error of the difference, and an actual difference of greater than twice the standard error was accepted as significant ($p<0{\cdot}05$). The χ^2 test was used where appropriate.

Results

ANGIOCARDIOGRAPHIC FINDINGS

The anterior descending artery was occluded in 101 patients (with or without a stenosis proximal to the occlusion), and narrowed by 90% of its diameter in 40, 80% in 24, 70% in 21, 60% in 12, and 50% in 20. The most proximal major lesion (greater than 50%) was in LAD1 in 81 patients, LAD2 in 104, and LAD3 in 33. Additional irregularities or minor stenoses (range 10 to 40%) were present in the right or circumflex arterial systems in 142 patients.

Satisfactory measurements of left ventricular ejection fraction were made for 201 patients. The mean ejection fraction was 59·2% (SD 19·2) in 74 with LAD1 lesions, 61·2% (SD 20·2) in 95 with LAD2 lesions, and 68·4% (SD 12·0) in 32 with LAD3 disease. The difference in mean ejection fraction between those with LAD1 and LAD2 disease is not statistically significant, but those between patients with LAD1 and LAD3 disease, and between those with LAD2 and LAD3 disease are significant

($p<0{\cdot}05$). Analysis of segmental wall motion disclosed a similar trend: the average number of abnormally contracting segments was 1·35 in the 81 patients with LAD1 lesions, 1·04 in the 104 with LAD2 lesions, and 0·58 in the 33 with distal (LAD3) disease. This progressive increase in the number of abnormal segments with more proximal obstruction is highly significant ($p<0{\cdot}01$).

In patients with previous infarction (based on the history or the electrocardiogram, or both) left ventricular function was more severely impaired, though the variation was wide. For the three groups, LAD1, LAD2, and LAD3 mean ejection fractions were 48·0% (SD 18·3) (n=40), 53·7% (SD 19·9) (n=44), and 68·2% (SD 15·4) (n=13), respectively (LAD1—LAD2 difference not significant, LAD2—LAD3 $p<0{\cdot}01$). The corresponding mean numbers of abnormally contracting segments were 2·13 (n=42), 1·82 (n=45), and 1·08 (n=13) ($p<0{\cdot}01$). Thirty-two patients, all with left anterior descending occlusion, had left ventricular aneurysms; in 11 the obstruction was in LAD1, in 19 it was in LAD2, and in two in LAD3. Left anterior descending occlusion was not invariably associated with clinically recognisable myocardial necrosis: 18 patients with occlusion (eight LAD1, five LAD2, and five LAD3) had no history or electrocardiographic evidence of infarction, and had normal ventriculograms.

CLINICAL PRESENTATION

In 73 patients (33%) the first manifestation of heart disease was a myocardial infarction. One hundred (46%) presented with exertional angina pectoris, 35 (16%) with angina at rest, two (1%) with breathlessness, and eight (4%) with "atypical" chest pain. At the time of angiography 164 had angina, 14 complained predominantly of breathlessness, eight had "atypical" pain, and 29 were symptom free. Three of the patients who presented with myocardial infarction were in cardiogenic shock. One hundred patients had at some time had a myocardial infarction.

In patients with angina at the time of coronary angiography there was no discernible relation between its severity and the site of left anterior descending obstruction; rest pain, for example, was present in 21% (12/57) of patients with LAD1, 21% (17/81) with LAD2, and 23% (6/26) with LAD3 lesions. By contrast, and consistent with the angiocardiographic analysis, clinical evidence of left ventricular failure was more common with proximal coronary obstruction: 12% of patients (10/81) with LAD1 disease were in left ventricular failure (three had cardiogenic shock), compared with 7% (seven/104) with LAD2, and 3% (one/33) of the LAD3 patients.

The resting electrocardiogram was normal in 82 patients (38%). In 60 (28%) there were ST segment or T wave changes, of whom two with T wave inversion in leads V1-V4 had complete right bundle-branch block. Q waves or poor R wave progression were present in 73 cases (33%) and in six this was associated with complete right bundle-branch block. One patient had complete atrioventricular block, and two were in atrial fibrillation. The proportion with electrocardiographic changes of infarction at the time of angiography was related to the site of the most proximal anterior descending lesion: 47% of patients (38/81) with LAD1 disease had these changes compared with 27% (28/104) of those with LAD2, and 21% (seven/33) of those with LAD3 obstruction ($p<0{\cdot}01$).

EXERCISE TESTING

Symptom limited graded exercise tests were carried out on a bicycle ergometer in 109 patients before cardiac catheterisation. Lead 1 of the electrocardiogram was monitored continuously and recorded at the end of each stage. The results are given in Table 1. In 25 of 41 patients (61%) with LAD1 lesions exercise was terminated by chest pain, 1 mm or greater ST segment depression 0·08 s after the end of the QRS complex, or by both pain and ST segment change. By contrast, only 21 of 51 patients (41%) with LAD2 lesions, and five of 17 (29%) with LAD3 lesions had these end-points ($p<0{\cdot}05$). The mean peak load was not significantly different between the three groups of patients.

COLLATERAL CIRCULATION

In seven patients of 101 with left anterior descending occlusion the distal vessel did not opacify during angiography, and no collateral vessels were seen. Left ventricular function was severely impaired in these patients including the three in cardiogenic shock: the mean ejection fraction was 28% (range 10 to 41%), and all had two or more abnormally contracting segments.

In the other 94 patients with occluded arteries the distal vessel was visualised during the left coronary injection. In 77 of these the vessel also opacified by visible collateral channels from the right side (or from the left, when the right coronary artery was non-

Table 1 *Exercise testing in 109 patients*

	LAD1	*LAD2*	*LAD3*
Mean peak load (kpm/min)	582	623	609
End-point			
Chest pain	11(2)	11(4)	3(0)
Dyspnoea	15(5)	22(6)	6(1)
Fatigue	13(7)	16(4)	6(1)
Other	2(2)	2(0)	2(0)
Total	41(16)	51(14)	17(2)

Figures in parentheses are patients with ST segment depression.

dominant). Most commonly these vessels were in the septum arising from the posterior descending artery, but in some cases an enlarged conus artery or a vessel around the cardiac apex in direct continuity from posterior to anterior descending arteries comprised the main collateral communication.

Collateral vessels were never seen in patients with less than 70% stenosis of the left anterior descending artery, even in the presence of clear historical, electrocardiographic, or ventriculographic evidence of previous infarction. Such communications opacified in one of 21 patients with 70% stenosis, in two of 24 with 80% stenosis, in 13 of 40 with 90% stenosis, and in 77 of 101 with occlusion. This tendency for the more frequent demonstration of collateral circulation with increasing arterial obstruction is highly significant ($p<0·01$).

Left ventricular function in patients having left anterior descending occlusion with opacified collateral channels was compared with that in patients with occlusion and no visible collateral circulation other than "ghosting" of the distal vessel. The mean ejection fraction was 59·2% (SD 17·5) in 73 patients with collaterals, and 44·7% (SD 25·5) in 17 without; the difference is significant ($p<0·05$). Wall motion analysis disclosed a similar difference: patients with visible collaterals had an average of 1·47 abnormal segments compared with 2·23 in those without ($p<0·05$).

There was no discernible relation between the demonstration of collateral vessels and the severity of angina. Of the patients with angina and opacified collaterals, 21% (15/71) had pain at rest, compared with a 23% (21/93) incidence of rest pain in those without collaterals on the angiogram. It should, however, be emphasised that eight of the 21 patients with rest pain and no demonstrable collaterals had left anterior descending stenoses of less than 80%.

It is widely believed that collateral vessels can grow in response to chronic ischaemia from slowly progressive arterial obstruction, thereby protecting the myocardium when occlusion finally occurs. An indirect attempt to examine this assumption was made in the patients with infarction and left anterior descending occlusion by comparing left ventricular function between those who presented with their infarction and those whose first clinical event was angina. In 49 patients presenting with infarction the mean ejection fraction was 44·2% (SD 20·6) compared with 56·6% (SD 9·6) in 23 patients in whom angina preceded infarction ($p<0·01$).

FOLLOW UP

Fifty-one patients (19 LAD1, 28 LAD2, and four LAD3) with severe angina (mean grade 2·8, 15 rest pain) had vein grafts to the anterior descending artery. There were no perioperative deaths or electrocardiographically recognised myocardial infarctions. One patient had a non-fatal inferior infarct 33 months after operation, one died suddenly after 77 months, and another died from carcinoma of the bronchus. At follow up three to 84 (mean 39) months after angiography, 38 (75%) were symptom free or had improved by at least two grades. Eleven patients (eight LAD1 and three LAD2) had left ventricular aneurysms resected; a patient with cardiogenic shock died 10 days after operation, and another died after 61 months. Six were symptomatically improved at follow-up.

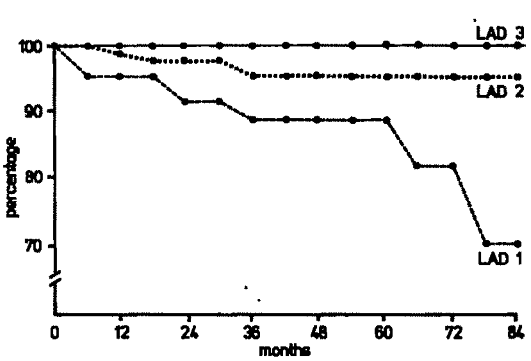

Fig. 2 *Survival curves of the patients classified according to the site of the most proximal anterior descending artery obstruction.*

Conservative management was adopted for the other 156 patients. Detailed follow-up information (three to 84, mean 24 months) is available on 99 of those who had angina at the time of angiography; 71% (22/31) of those with LAD1, 52% (24/46) with LAD2, and 82% (18/22) with LAD3 disease were symptom free or improved. Nine medically treated patients died, all from their heart disease. In six the most proximal obstruction was in LAD1, and in three in LAD2 (one LAD2 equivalent); none with disease confined to the distal vessel died. In general the left ventricular function of those who died was poor at the time of cardiac catheterisation: their mean ejection fraction was 38% (range 10 to 83%), and they had an average of 2·64 abnormally contracting segments. Four, including two with cardiogenic shock, had severe left ventricular failure.

Details of patients who died (excluding the non-cardiac death) are given in Table 2, and the combined medical and surgical survival curves are plotted in Fig. 2. Overall, nine out of 81 patients (11%) with LAD1 disease died compared with three out of 104 (3%) with LAD2 disease, and none of the 33 with distal lesions. Despite the small number of deaths, the difference in mortality between LAD1 and LAD2

Table 2 *Mortality: clinical and angiocardiographic details*

	LAD lesion	*LV function*		*Presentation*	*Electrocardiogram*	*Survival (mth)*	*Collaterals*	*Comments*
		Ejection fraction (%)	*No. of abnormal segments*					
1	1 occlusion	50	3	AP 3	Poor R	33	Present	
2	1 occlusion	29	3	MI, CS	Q	0	Absent	
3	2 occlusion	10	3	MI	Poor R	35	Present	
4	2 80%	47	3	MI	T inversion	10	Absent	
5	1 occlusion	52	2	AP 3	Q	20	Present	
6	1 occlusion	10	3	MI, CS	Q	0	Absent	
7	* 3 occlusion diag. 70%	83	0	AP 3	T inversion	14	Present	
8	1 70% 2 occlusion	52	2	AP 2	CHB	0	Present	Paced
9	1 occlusion	27	3	MI	Poor R	23	Present	
10	1 occlusion	21	3	MI, CS	Q	0	Absent	Aneurysmectomy
11	1 occlusion	38	4	MI	Q	61	Present	Aneurysmectomy
12	1 occlusion	34	3	MI	Q	77	Present	Vein graft

*LAD 2 equivalent; diag., diagonal branch; AP, angina pectoris; MI, myocardial infarction; CS, cardiogenic shock; Q, anterior Q waves; CHB, complete heart block.

patients, and between both LAD1 and LAD2, and LAD3 is statistically significant ($p<0.05$).

Discussion

In this study of patients with clinically manifest coronary disease confined to the anterior descending artery, those with proximal lesions had on average greater impairment of left ventricular function than those with more distal obstruction. These observations confirm those of two recently reported studies of patients with anterior myocardial infarction from which it was concluded that the site of left anterior descending obstruction was a primary determinant of the size of the infarction.[8 9] We have shown in addition that the prognosis of our patients was related to the site of the obstruction, but because some had surgical treatment which might itself have influenced the outcome, we cannot be certain that this represents the untreated natural history. To alter this relation, however, surgery would have had to prevent death in patients with distal lesions, and this seems unlikely. The worse prognosis of left anterior descending obstruction proximal to the first septal branch in comparison to that of more distal lesions is well recognised,[10 11] but has not previously been shown to hold for patients with disease confined to the left anterior descending artery.

Despite overall differences in left ventricular function (and indirectly in prognosis) between patients with obstruction in different parts of the left anterior descending artery, a number with proximal occlusion had little or no ventricular damage while others with distal disease had had extensive infarctions. Two questions remain unanswered: what factors other than the site of obstruction determine the potential area of infarction, and is it logical to expect that by expanding the indications for aortocoronary bypass surgery the prognosis could be improved?

One possible explanation for the great variability in extent of myocardial necrosis which accompanies left anterior descending occlusion is that the functional capacity of the collateral circulation might vary from one person to another, and indeed from one moment to another in the same patient. Though there were patients with "good" collaterals and extensive infarction we observed an overall association between the failure of their angiographic opacification and severe left ventricular damage. Similar observations have been made by other authors,[12–14] but we believe that their assumption of a cause and effect relation between angiographically assessed "inadequate collateral vessels" (sic)[12] and extensive infarction may be an oversimplification. Widespread necrosis might result in destruction of collateral vessels or of the capillary bed they perfuse, or in their functional closure because of the lower metabolic demand of fibrous tissue compared with that of contracting myocardium. Furthermore, collateral filling might not occur because the perfusion pressure (the difference between proximal and distal coronary pressure) at the time of angiography was not sufficiently high—this could arise from a low arterial pressure, from a high left ventricular diastolic pressure (present in the patients with "inadequate collateral vessels" described by Williams *et al.*[14]), or from a combination of the two. In support of this theory is our observation that collateral vessels were never seen when the left anterior descending stenosis was less that 70% (distal coronary pressure too high). Furthermore, when coronary stenoses are treated by angioplasty collateral vessels immediately "disappear" with relief of the obstruction and they may "appear" promptly with the development of occlusive coronary artery spasm. These considerations together with our inability to discern a relation between the severity of angina and demonstrable collateral filling suggest that angiographic visualisation of the collateral circulation discloses limited information concerning its functional potential.

On the other hand, the observation that left ventricular function was more severely impaired in patients with left anterior descending occlusion who presented with infarction than in those who presented with angina and subsequently had an infarction supports the belief, based on post-mortem studies,[15 16] that collateral vessels can increase in size in response to slowly developing ischaemia, and that they confer a protective effect. Finally, it is possible that the occurrence and extent of necrosis caused by closure of a coronary artery is dependent also on the autonomic and consequent haemodynamic disturbances accompanying the event, which influence not only collateral flow, but also the myocardial oxygen consumption.

Because this is a retrospective study and 30% of the patients had operations, we are not in a position to draw more than the most tentative conclusions about the role of surgery. There is, however, nothing to support the view that aortocoronary bypass would improve the prognosis of those with proximal lesions who are symptom free or who have only mild angina. Mortality is related to left ventricular function and 11 of the 12 patients who died had angiocardiographic evidence of extensive infarction (two or more abnormally contracting segments) at the time of presentation and investigation. Only one patient with a normal left ventricular angiogram died. It is possible that the prognosis of the 51 patients with severe angina who had vein grafts has been improved by the operation. In view of the undoubted benefit of surgical treatment in terms of pain relief, however, it is doubtful whether such a proposition can ever be put to the test of a formal trial.

The short-term prognosis for most patients with isolated disease of the anterior descending artery is, therefore, good, a conclusion that confirms earlier reports. The outcome is influenced by the site of obstruction, and may be ameliorated by growth of the collateral circulation stimulated by recurrent ischaemia. Severity of angina at presentation is not a good indication of the site of left anterior descending disease, though exercise testing may give useful information. While our findings support the view that management of patients with coronary disease should be governed by the amount of myocardium at risk, a factor determined only in part by the number of vessels involved, there is no evidence to support the contention that isolated proximal anterior descending artery obstructions should be bypassed unless this is required for relief of limiting angina.

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Strong family history and cigarette smoking as risk factors of coronary artery disease in young adults*

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SUMMARY This study is based on 435 consecutive patients age 50 or less who had coronary arteriography. There were 335 patients with coronary artery disease and 100 with normal coronary arteries. Risk factors reviewed were "packet-years" of cigarette smoking, family history of coronary disease in first-degree relatives 50 years of age or less, age- and sex-corrected serum cholesterol and triglycerides, hypertension, and diabetes. By univariate analysis, each risk factor except hypertension and diabetes was significantly more frequent in patients with coronary disease than in those without. By multivariate analysis of all risk factors in patients with and without coronary disease, the male or female patient with coronary disease could best be identified by the strong family history, cigarette smoking history, and age- and sex-corrected serum cholesterol. The percentage of patients with coronary disease when the three risk factors were present was 95%, two factors present 88%, one factor present 67%, none of the three 25%, strong family history alone 90%, smoking alone 66%, and serum cholesterol >80th centile alone 52%.

Coronary atherosclerotic disease starts at a young age and takes many years to progress into the symptomatic stage.[1] By the time the first symptom appears, the disease is advanced to two- or three-vessel involvement in most patients,[2] and indeed sudden death may be the first symptom in nearly one-third of patients.[3] It is imperative that these patients be identified at a young age before the first symptom appears, for it is at the early stages of the disease, rather than in the later symptomatic stages, that intervention to prevent progression of disease and death is most likely to be successful. Furthermore, when the disease appears at a young age, it might be more rapidly progressive unless interventions are made. Improvement in identification of the large majority of young persons in the general population at high risk of developing coronary disease by noninvasive methods is needed. As a first step in approaching this problem we have reviewed the risk factors in 435 patients 50 years of age or younger who had coronary arteriography.

Patients and methods

Patients selected for study included consecutive Caucasian patients of 50 years of age or less who had coronary arteriography because of typical or atypical chest pain from 1 July 1975 to 30 June 1977. The patients were divided into two groups: (1) 335 patients with coronary artery disease (median and mean ages 46 and 45 years respectively, 88% men) who had at least one coronary artery stenosed >50% in luminal diameter (138 or 41% had previous myocardial infarction) and (2) 100 patients (median and mean ages 44 and 43 years respectively, 58% men) who had angiographically normal coronary arteries, no previous myocardial infarction by history or electrocardiographic criteria, and no clinical evidence of peripheral arteriosclerosis obliterans as judged by normal arterial pulses and absence of claudication and bruits. Patients with coronary lesions <50% in luminal diameter, and associated valvular, congenital, or cardiomyopathic heart disease were excluded.

RISK FACTORS

The following risk factors were considered.

(1) Cigarette smoking

The number of "packet-years" (number of packs (20 cigarettes per pack) per day times number of years smoked) of smoking was determined from the patient as previously described and along with the current smoking status (smoking within a week before coro-

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nary arteriography). In the text we will use number of years of smoking to mean the numbers of packet-years of smoking.

(2) Family history
We only considered a strong family history of coronary disease (myocardial infarction, sudden death, exertional angina, or disease documented by coronary angiography) in first-degree relatives who were age 50 years and under as previously described.[4]

(3) Hyperlipidaemia (at the time of admission for coronary arteriography)
Hypercholesterolaemia and hypertriglyceridaemia were analysed as previously described[4] and defined as at or above the 95th or 80th centile* for a patient's age and sex, and for discriminant function analysis as the age- and sex-corrected serum cholesterol and triglyceride relative deviate.

(4) Systemic hypertension
This was taken as positive if the diagnosis (>160/95 mmHg) had been made before coronary arteriography (and patients were susequently given antihypertensive medication) or if at the evaluation for coronary arteriography the blood pressure was ≥160/95 mmHg on three occasions.

(5) Diabetes mellitus
This was defined as two fasting plasma glucose values ≥6·6 mmol/l (≥120 mg/dl) normal ≤5·5 mmol/l (normal ≤100 mg/dl) or insulin dependence.

CORONARY ARTERIOGRAPHY
Selective coronary cineangiography was performed with and without cranial angulation and as previously described.[5] Patients with a maximal coronary artery stenosis <50% (22 patients) were excluded from the study to make the division between coronary disease and normal coronary arteries as definite as possible.

STATISTICS
Significance of univariate analysis of risk factors was tested by Student's t test or χ^2. Stepwise linear discriminate function analysis was carried out according to the RMD P7M computer program of the Health Sciences Computing Facility, University of California at Los Angeles.

Results

PREVALENCE OF RISK FACTORS
The Figure shows the percentage of patients with each risk factor for those with and without coronary artery disease. Each risk factor except hypertension and

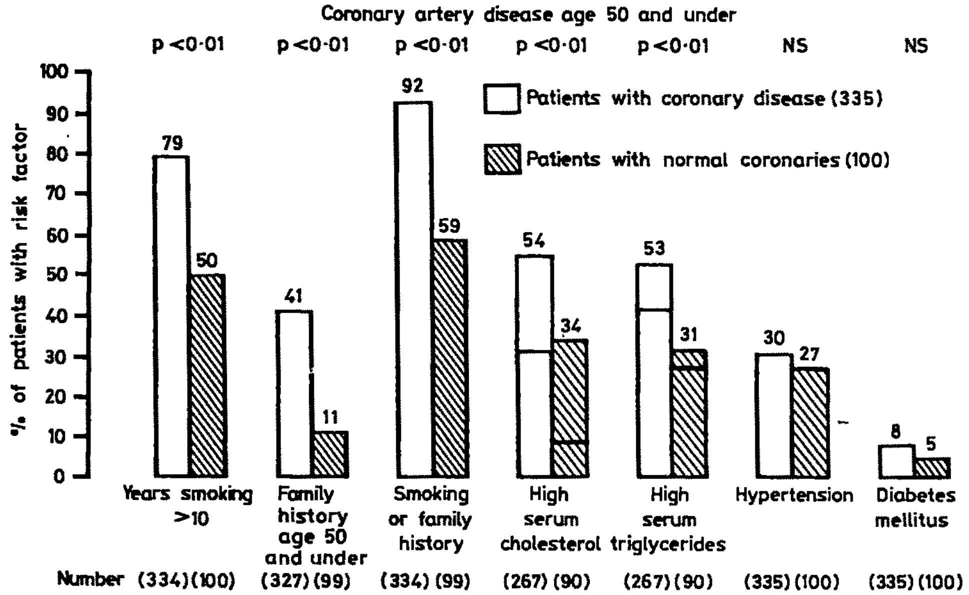

Fig. *Univariate analysis of risk factors in young patients with coronary artery disease and those with normal coronary arteries. Serum cholesterol and serum triglycerides were taken at ≥80th centile for age and sex (top of bar) and 95th centile (solid line in bar). Not shown is current smoking status for coronary disease (26%) and normal coronary (22%) patients. Each risk factor except diabetes, hypertension, and current smoking status was significantly (p<0·01) more frequent in patients with coronary disease than in those without. Number of patients in each risk factor subgroup is shown below each bar. Patients in whom a risk factor was unknown were excluded from analysis: smoking 1, family history 8, cholesterol and triglycerides 68 (coronary disease), and 10 (normal).*

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*Age-sex specific centiles were established by our laboratory on the basis of 458 carefully screened healthy adults. At age 45 the 80th centiles (in mg/100 ml) for cholesterol were 250 for men and 235 for women, and the 95th centiles were 285 in men and 267 in women. For triglycerides the 95th centiles at age 45 were 195 in men and 125 in women.

diabetes mellitus was present in a significantly (p<0·01) higher percentage in the patients with coronary artery disease. Cigarette smoking was the single most frequent risk factor in patients with coronary disease, being present in 79% of the patients. Family history of coronary artery disease at a young age was found in 41% of patients with coronary artery disease and only 11% of normal patients. A cholesterol level at or above the 95th centile was found in 31% of patients with coronary disease and 9% of patients with normal coronary arteries. A triglyceride level at or above the 95th centile was found in 41% of patients with coronary disease but also in 27% of normal patients. We also looked at the percentage of patients with cholesterol and triglyceride levels at or above the 50th and the 80th centiles for age and sex (Fig. and Table 1). The presence of a history of cigarette smoking or a positive family history (or both) was found in 92% of patients with coronary disease and 59% of patients with normal coronary arteries (Fig.).

Table 1 *Risk factor prevalence in patients with and without coronary disease at different cut points in three of the continuous variables: the patients are those in whom all risk factors were available for analysis.*

	Males		*Females*		*Total*	
n=351	CAD 232	No CAD 53	CAD 30	No CAD 36	CAD 262	No CAD 89
	%	%	%	%	%	%
Age <40	16	40	10	17	15	27
Family history	41	11	37	8	40	10
Packet-years						
0	16	21	20	69	17	40
≥10	79	68	73	28	79	52
≥30	49	32	40	8	48	22
Cholesterol						
>P_{50}	81	58	87	58	82	58
>P_{80}	53	34	60	33	54	34
<P_{95}	28	6	47	11	30	8
Triglyceride						
>P_{50}	86	66	77	83	85	73
>P_{80}	51	30	70	33	53	31
>P_{95}	39	25	57	31	41	27
Hypertensive	30	40	10	17	28	30

PREDICTIVE VALUE OF RISK FACTORS

Linear discriminant analysis

Stepwise linear discriminant function analysis in the 351 patients in whom all the risk factors were available for analysis (family history, number of packet-years of cigarette smoking, current smoking status, age- and sex-corrected cholesterol and triglyceride levels, hypertension, systolic blood pressure, diastolic blood pressure, and diabetes mellitus) showed that the young patient with coronary artery disease could best be identified by cigarette smoking, family history, cholesterol, sex, and age. Table 2 summarises the results of stepwise linear discrimination between those with and those without coronary artery disease for men, women, and the total group and lists the variables selected in order of their discriminating power. Sex-corrected cholesterol, strong family history, and packet-years of cigarette smoking were selected by linear discriminant function in both sexes. Age was not selected in women probably because of the smaller age spread (see Table 1).

Table 2 *Stepwise linear discrimination between those with and without coronary disease*

(*N*=*351*)	*Men*	*Women*	*Total*
Selected* by linear discriminant function	Chol Age Fam. Hx. Packet-years+	Packet-years Chol Fam. Hx.	Sex Chol Fam. Hx. Packet-years Age

N, number of patients.
*Using F to enter ≥4 (p<0.05) when age is dropped.
Fam. Hx., strong family history; Packet-years, number of packet-years of cigarette smoking; Chol, age- and sex-corrected serum cholesterol relative deviate.

Univariate analysis

Table 3 describes the coronary disease prevalence in eight subgroups defined in terms of strong family history, cholesterol level above the 80th centile for age and sex, and 10 years or more of cigarette smoking in the 351 patients (262 with and 89 without coronary disease) for whom data on all three of these risk factors were available. When none of these risk factors are present 25% of patients have coronary disease, with one of these factors 67% have coronary disease, with two of these factors 88% have disease, and the increase is small (88% to 95%) with a third risk factor.

Table 3 *Coronary disease prevalence in subgroups defined by family history, cigarette smoking, and cholesterol risk factors*

Family history	Cholesterol >P_{80}	≥10	N	% CAD
+	+	+	42	95
+	−	+	32	97
+	+	−	19	79
−	+	+	83	87
+	−	−	21	90
−	−	+	95	66
−	+	−	27	52
−	−	−	32	25
			351	

N, number of patients; CAD, coronary artery disease.

Strong family history is the single risk factor that is associated with the greatest prevalence of coronary disease (90%), followed by ≥10 years cigarette smoking (66%), and cholesterol level above the 80th centile (52%). These above results would change if the cut points for centile of cholesterol and number of years of cigarette smoking were changed. Table 1 describes the results in the same 351 patients included in Table 3 without regard to subgroup analysis but at different cut points for centile cholesterol and triglycerides and number of years of smoking.

Discussion

This study clearly shows the association between the strong family history, cigarette smoking, and age- and sex-corrected cholesterol risk factors and the presence of coronary disease in young patients having coronary angiography. These are factors of recognised importance in the development of coronary artery disease in the general population, but the strong family history risk factor (in first degree relatives at age 50 and under) is not widely recognised and has not frequently been looked for in large prospective epidemiological studies. While it is not surprising that the association penetrates to this angiographic subgroup, the strength of the association may have been materially altered by the selection process of patients for coronary angiography. A safe, noninvasive measure of the degree of coronary stenosis comparable in accuracy to angiography could determine the strength of this association in the general population, but such a noninvasive method is not yet available.

Studies aimed at risk factor prediction of the presence or absence of coronary disease which involve individuals who are candidates for coronary arteriography have the advantage of eliminating the misclassification which results from errors of clinical diagnosis.[6] Individuals who have had coronary arteriography, however, do not necessarily represent the general population since, on the one hand, those with coronary disease and no symptoms of coronary disease are underrepresented, and those who die at the initial event are missing. Though the subgroup with normal coronary arteries is missing those with no symptoms, this subgroup has been shown, when restudied after 12 to 104 months, to have a benign prognosis[7] and normal coronary arteries.[8] [9] This group was also free of clinical peripheral atherosclerotic disease.

It is difficult to establish the precise order of importance of the three major risk factors. For a single risk factor, strong family history is associated with the largest increase in coronary disease prevalence, and years of smoking is next (Table 3). By stepwise linear discrimination all three are significant in identifying the coronary patient, but cholesterol ranks ahead of the other two in men and in the total group while years of smoking ranks first in women (Table 2). In univariate analysis the three risk factors are all highly significant. For example, using strong family history, the difference in the percent positive gives $\chi_1^2=27$, cigarette smoking ≥30 years gives $\chi_1^2=18$, and cholesterol above the 90th centile for age and sex also gives $\chi_1^2=18$. The method of statistical observation and the cutoff point used for a continuous variable may change the order of apparent importance. We found from practical and clinical standpoints that it is uncommon to find a patient 50 years of age or younger with angiographically proven coronary artery disease who does not have a cigarette smoking history or a positive family history of coronary artery disease at a young age. It is also uncommon to find angiographically normal coronary arteries in a young person who has both of the latter risk factors or all three of these risk factors (≤5%) as noted in Table 3.

Cigarette smoking is a well-recognised primary risk factor[10] [11] in men[12] and women[13] and a recently recognised cause of secondary complications in patients with known coronary artery disease who continue to smoke, compared with former smokers or nonsmokers.[11] [13] We found that a history of 10 years or more of cigarette smoking increases the risk of having coronary artery disease whether or not the patient is currently smoking. Thus, in taking the history it is important to determine a quantitative estimate of previous cigarette smoking since only a small number of patients may be currently smoking. We observed only 26% of patients with coronary disease and 22% of patients with normal coronary arteries to be currently smoking. The mechanism whereby smoking contributes to the development and complications of coronary artery disease is unknown but is discussed by us elsewhere.[4] Unfortunately, there is an alarming trend toward increased smoking in women and young people,[14] and, therefore, better methods leading to prevention and cessation of smoking are needed.

It is important to note the strength of the family history risk factor in a patient's history since the occurrence at a young age appears to be associated with coronary disease in other young family members who present with symptoms of possible coronary disease. It is of interest that clinical manifestations of coronary disease show similarities within sibships such as cardiac deaths being most common in sibs of the fatal infarction probands.[15] The younger the age at diagnosis the greater the risk of premature coronary disease in other first-degree relatives.[16] Slack and Evans[17] found that the risk of coronary death under age 55 is 5·2 times that of the general population if a male first-degree relative has died from coronary disease under age 55, and 2·8 times if the relative is a women under age 65. These increases in risk are about twice that experienced by middle-aged men with serum cholesterol over 7·8 mmol/l (300 mg/dl) or diastolic blood pressure over 105 mmHg.[18] Since the strong family history risk factor is dependent on sibship size and birth order of the subject in relation to sibs, the absence of sibs or the subject being oldest among sibs, would probably lead to understimation of the frequency of this risk factor. The genetic factor that contributes to the development and progression of coronary artery disease is unknown, can only be speculated upon, and is discussed by us elsewhere.[4] Unlike studies from the Finnish population[19] we found that those with and without a positive family history did not differ significantly in any of the other risk factors. We found the cholesterol and triglyceride distributions for patients with a positive and those with a negative family history of coronary artery disease were not significantly different. In addition, in the subgroup of patients with both strong family history and cigarette smoking regardless of serum cholesterol, 96% (71/74) had coronary artery disease. It is also striking that 90% of patients with the strong family history risk factor alone had coronary disease. Asymptomatic young adults with the strong family and/or the cigarette smoking risk factors have a high incidence of a shortened ^{51}Cr platelet survival half-life suggesting enhanced platelet-arterial wall interaction[4] and the possibility that these individuals with risk factors and/or shortened ^{51}Cr platelet survival half-life may have subclinical atherosclerotic disease and might be good candidates for an early intervention trial in the "prevention" of coronary artery disease.

Hypercholesterolaemia is a well-documented primary risk factor[10 11] and a recently documented secondary risk factor[20] of coronary artery disease. Lowering of serum cholesterol may retard angiographic progression of coronary artery disease[21] and reduce mortality from coronary artery disease.[22] The increase in coronary artery disease with increasing serum lipid concentrations holds over the entire range, without any critical serum level to separate risk from non-risk groups.[23] The association was stronger with cholesterol than with triglyceride. Premature or accelerated atherosclerosis occurs in patients who have hyperlipoproteinaemia, but hyperlipoproteinaemia, as we also observed, is neither necessary nor sufficient for atherosclerosis.[24] Because the incidence of coronary artery disease and the levels of serum cholesterol in presumably healthy persons in the United States are higher than those in most countries of the world (including countries where smoking is prevalent), cholesterol may play a permissive role in the development of atherosclerosis. For example, in Japan, where smoking is very prevalent, the levels of serum cholesterol and the incidence of coronary artery disease are very low.[25]

Hypertension is both a primary[10] and a secondary[11] risk factor. In the two groups of young patients having angiography, we found no difference in the proportion with hypertension. It is possible that if we had been able to integrate the level of increase over time, an association might have been found. In addition, some of those with the longest duration of high levels of blood pressure might have been lost by death at the intitial manifestation of coronary artery disease (sudden death or fatal myocardial infarction).

Although these risk factors identify groups at high risk for having coronary artery disease at a young age, they are not as specific as coronary arteriography for identification of coronary disease. Not all risk factors, however, have necessarily been identified. The angiographic groups offer an opportunity for intensive studies to identify new risk factors. Since platelets appear to play a role in the development of atherosclerotic disease, we evaluated the relation between the risk factors found here and platelet consumption as assessed by ^{51}Cr platelet survival half-life.[4] We are also following medically treated coronary disease patients in a prospective, randomised, double-blind, platelet inhibitor drug trial, and will be able to see if the strong family history risk factor or platelet survival half-life are secondary risk factors in the angiographic progression of coronary artery disease.[26]

Thus, the strong family history is an independent risk factor not associated with a clustering of other risk factors. It helps identify young patients at risk of having coronary disease along with the cigarette smoking history and serum cholesterol and appears to be associated with enhanced platelet-arterial wall interaction.[4]

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Coital blood pressure in hypertensives
Cephalgia, syncope, and the effects of beta-blockade

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SUMMARY During the continuous monitoring of intra-arterial blood pressure in ambulant hypertensive subjects, 18 episodes of coitus were recorded in 11 subjects. Peak values of up to 300/175 mmHg were found, the mean for men being 237/138 mmHg and for women 216/127 mm Hg. Two patients with coital symptoms (cephalgia and syncope) showed no unusual responses and, when restudied after beta-blockade, one subject showed no reduction in peak coital blood pressure. The results complement those found previously in normal subjects and demonstrate the potential of the technique in investigating coital symptoms.

Sexual intercourse is occasionally associated with worrying symptoms or serious and even fatal complications. Attempts to define physiological changes therefore seem highly desirable, and have indeed been made by Masters and Johnson[1] among others. The recording of physiological variables during coitus under laboratory conditions, however, creates an unnatural setting which may produce distorted results.

In the investigation of patients with hypertension, we have performed a large number of ambulatory recordings of intra-arterial pressure. Subjects were encouraged to behave as normally as possible, being little encumbered by the monitoring apparatus, and several had sexual intercourse during the recording period. We report here the heart rate and blood pressure changes during coitus in these subjects and also in two subjects monitored specifically to investigate symptoms related to coitus. Results from a subject who had coitus during an inital study and also during a restudy after treatment with a beta-adrenoceptor blocking agent are also reported.

Methods

Subjects with suspected or established hypertension who had been referred to the hypertension clinic at the hospital were asked to volunteer for a period of ambulatory intra-arterial blood pressure monitoring. They were asked to behave normally but encouragement to have coitus was not specifically given except to two subjects who complained of symptoms related to coitus. The experimental procedure for these studies was approved by the Hospital Ethical Committee.

The monitoring equipment consisted of a revised version[2] of a system initially developed in Oxford.[3] A cannula was inserted percutaneously under local anaesthesia into the non-dominant brachial artery of the subject and joined by fine-bore tubing to a transducer/perfusion device. Signals from this and from adhesive chest electrocardiographic electrodes were recorded on two channels of cassette tape using a miniature recorder ("Medilog", Oxford Medical Systems). Enough wire was provided to allow the subject to position the recorder either behind him or at his side when lying flat. No event-marking system was used during these recordings but the time of occurrence of intercourse was recorded in the subject's diary. The system was calibrated each morning and evening during the recording.

In accordance with our standard procedure all tapes were written out in full using a pen-recorder (Lectromed). Episodes of sexual activity were easily identified and later replayed at faster paper speed using a fibreoptic recorder (Medelec Ltd). The nearest calibration signals were written out using the same system on an identical setting. The mean blood pressure and heart rate during the one minute before fluctuations associated with sexual activity were taken as precoital recordings and the highest levels sustained for five or more beats as "peak coital" values.

Results

Technically satisfactory recordings of coital blood

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pressure were made on 18 occasions involving 11 hypertensive subjects, representing 1·5% of all studies performed during this period. The mean age of the subjects was 42 years (range 29–56 years). The group included three women. The details of the patients and their recorded heart rates and blood pressures are shown in Tables 1 and 2.

The recordings showed that both heart rate and blood pressure fluctuated widely during sexual activity occasionally reaching very high levels. Though patterns varied greatly the highest peak of heart rate and blood pressure (presumably associated with orgasm) were generally simultaneous and were followed by a rapid fall to precoital levels or below. Examples of recordings can be seen in Fig. 1 (men) and Fig. 2 (women). All men achieved orgasm but only one of the women was known to have done so (case 10). Case 5 did not achieve orgasm and details for case 1 were insufficient.

Peak blood pressures were very high, the mean being 237/133 mmHg (range 184 to 300/92 to 175 mmHg) for men and 216/127 mmHg (range 190 to 260/110 to 155 mmHg) for women (Table 1 and 2). These levels were sustained in each case for only a few seconds. Peak heart rates were 131 beats/minute and 96 beats/minute for men and women, respectively.

Case reports

CASE 2

A 42-year-old Australian was referred because of "blinding" global headaches lasting between 10 minutes and one hour, precipitated only by sexual intercourse with extramarital partners. Examination was normal except that his blood pressure was moderately raised (165/115 mmHg). Routine investigations including urinary catecholamine excretion were normal.

An ambulatory blood pressure recording lasting 36 hours was undertaken during which he achieved orgasm five times. As can be seen from Table 1, the highest pressure experience (243/151 mmHg) was during intercourse with his wife. No headaches occurred during the recording and maximum pressures were within the range shown by asymptomatic hypertensives. Antihypertensive medication was prescribed (propranolol 80 mg bid and cyclopenthiazide 0·25 mg daily) and despite no loss of sexual function, headaches did not recur. He remains well, normotensive, and free from headaches, three years after the study.

CASE 5

This housewife of 39 years was referred for investigation of syncopal attacks. Borderline hypertension was noted (130 to 150/95 to 110 mmHg) and screening investigations including electrocardiogram and electroencephalogram were all normal. Attacks of dizziness increased in frequency, some coming on without warning and leading to unconsciousness and generally lasted for about three minutes. Her husband reported no signs of epileptic convulsions and empirical treatment with propranolol, digoxin, procainamide, or phenytoin did not affect the attacks, the only consistent trigger of which was sexual intercourse.

Outpatient electrocardiographic monitoring spanned a typical attack but no arrhythmia was detected. A period of 48 hours of ambulatory blood pressure monitoring was carried out during which a typical attack with loss of consciousness followed sexual intercourse (no orgasm); the record is shown in Fig. 2b. No arrhythmia or period of sustained or pronounced hypotension was apparent.

The patient was strongly reassured and treatment (cyclopenthiazide 0·5 mg daily) given for the hypertension. Over the subsequent two years the attacks decreased in frequency and their description seems to indicate a non-organic nature.

CASE 7

This 29-year-old agricultural research worker had sexual intercourse twice during a routine ambulatory blood pressure assessment after borderline clinic readings. He was later treated for hypertension (sotalol 80 mg tid) and on a subsequent recording he had sexual intercourse again. All three episodes occurred in the early afternoon and the subject felt them to be comparable. Peak coital values of heart rate and blood pressure achieved during the restudy were between those found during the two pretreatment episodes, despite both clinic and mean ambulatory measurements indicating satisfactory blood pressure reduction (see Table 1).

Discussion

Sexual intercourse probably affects the cardiovascular system by a number of component methods. There are certainly elements of both isometric and dynamic exercise, breath-holding episodes, and psychological stress, all of which are known to increase heart rate and blood pressure. In addition there is the general activity of autonomic reflexes necessarily involved in arousal, erection, orgasm, and ejaculation. That sexual arousal, as opposed to other strong emotions, produced consistent rises in heart rate and blood pressure in young men was shown by Scott in 1930.[4] Later workers[1 5 6] have shown the extreme magnitude of these changes in some subjects when monitoring covered the period of orgasm. All these studies, however, were carried out under laboratory conditions and subject to the potential sources of bias

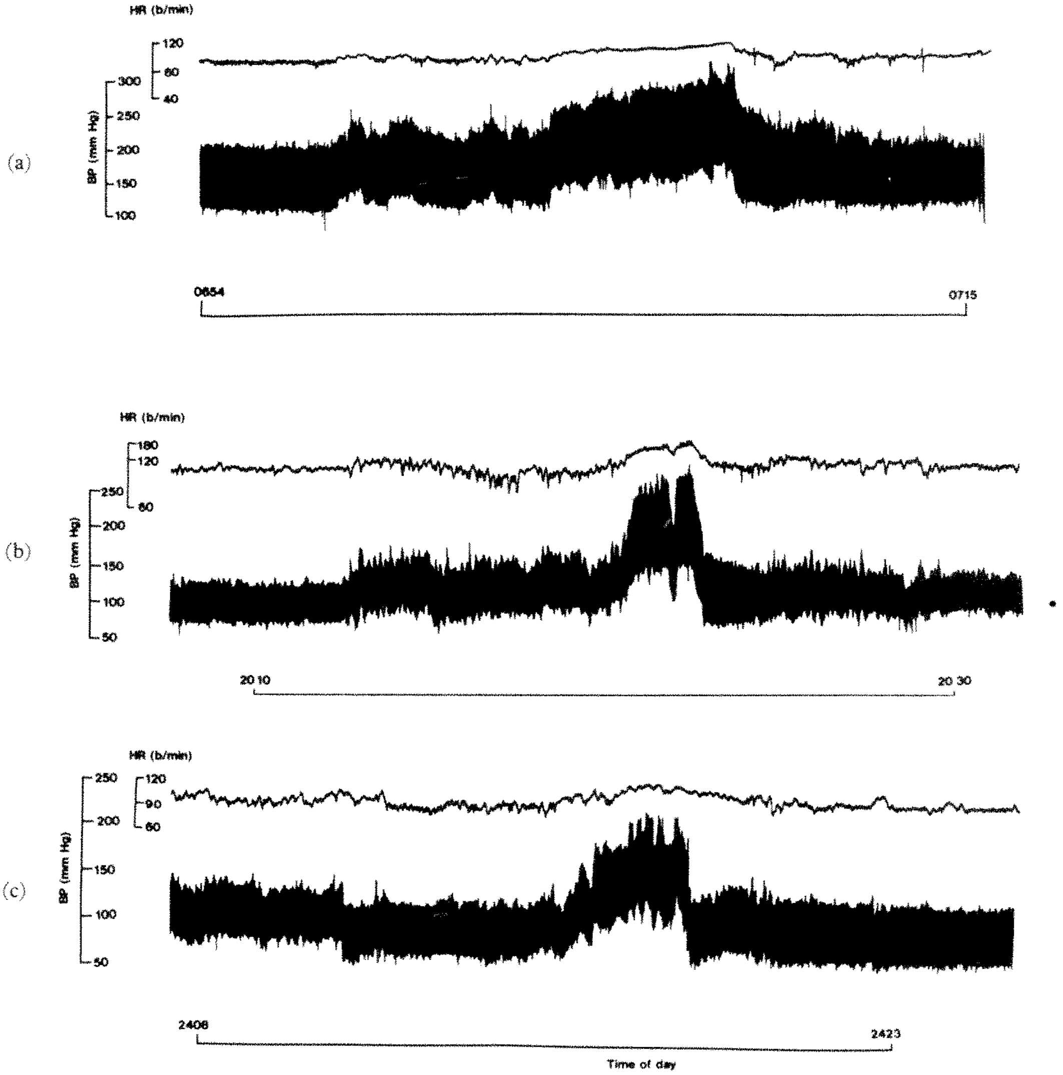

Fig. 1 *Examples of coital blood pressure recordings in three hypertensive men: (a) case 2; (b) case 6; (c) case 8. Note the widely fluctuating pattern and simultaneous peaks in heart rate and blood pressure at the time of presumed orgasm.*

mentioned earlier. When Hellerstein and Friedman[7] monitored the ambulant electrocardiograms of middle-aged patients with ischaemic heart disease they found that the peak coital heart rates were much lower than those expected from laboratory results.

The rapid changes in heart rate and blood pressure also indicate the need for a measuring system using continuous monitoring; the value of intermittent non-invasive measurements is clearly questionable. Littler *et al.*,[8] using monitoring equipment similar to ours, reported heart rate and blood pressure in six men and one woman (all normotensive), and showed that intra-arterial pressures of up to 233/128 mmHg were achieved during coitus. From our study it is apparent that those subjects starting with higher baseline levels reached correspondingly higher peak pressures during coitus.

It is possible that pathological cardiovascular events

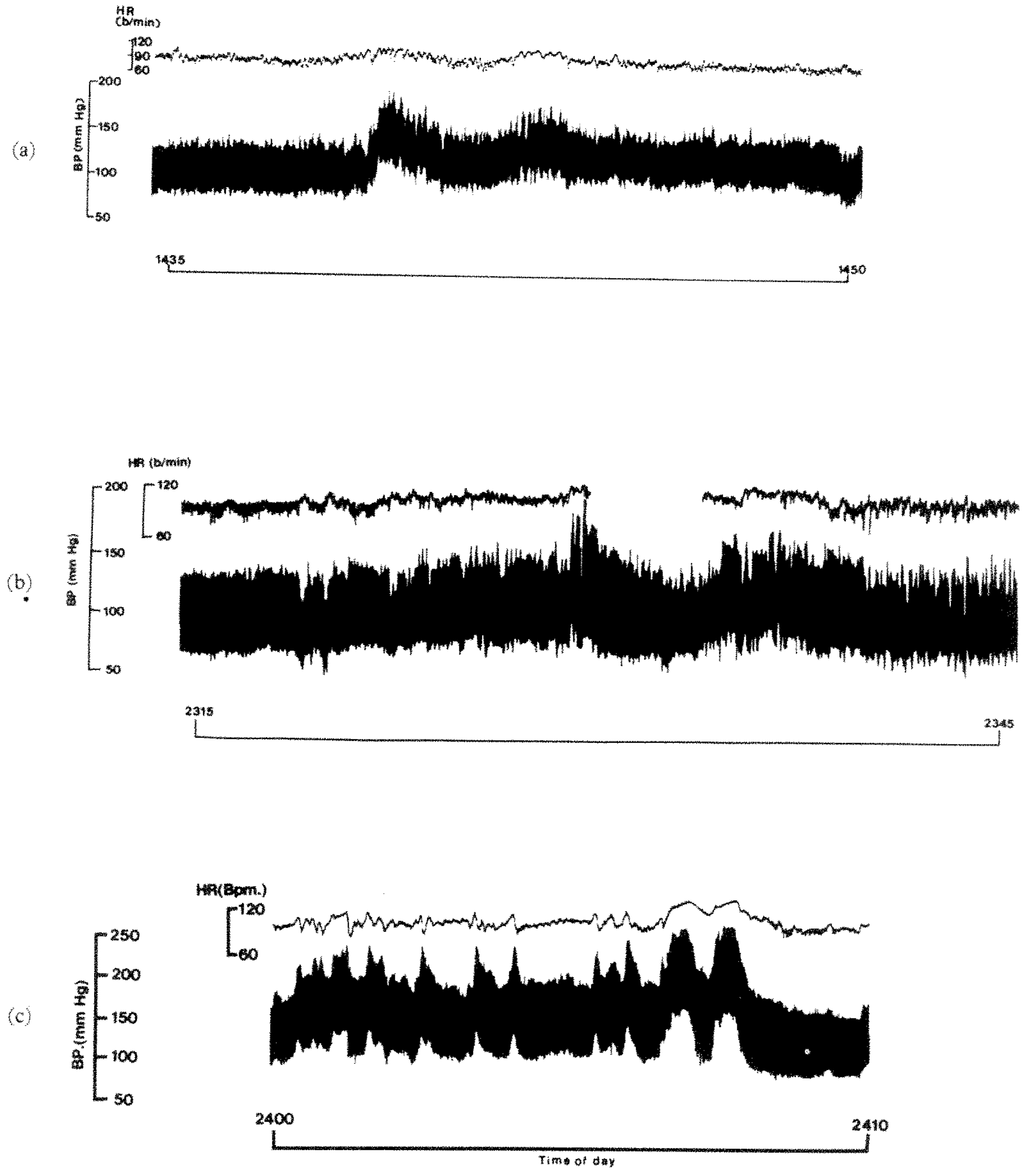

Fig. 2 *Examples of coital blood pressure recordings in three hypertensive women: (a) case 1 (orgasm not recorded); (b) case 5 (no orgasm, coital syncope); (c) case 10 (orgasm).*

occur directly as a result of high peak pressures in hypertension (or ischaemic heart disease) and, if so, the implications for management, both in terms of behaviour modification and antihypertensive medication, are profound. Such events known to be associated with sexual activity include angina pectoris, myocardial infarction, sudden cardiac death, cerebral haemorrhage, and other neurological symptoms. Though anecdotal evidence for the occurrence of the more serious complications is common, epidemiological surveys [9–11] suggest that this is not the case. Recurrent and worrying symptoms are also uncommon but may, as exemplified by cases 2 and 5, present problems of diagnosis.

Coital cephalgia, noted by Hippocrates[12] and documented more fully in recent years, may occasionally be a manifestation of subarachnoid haemorrhage[13 14] but more usually appears to follow a benign

Table 1 *Details of patients and coital blood pressure levels in eight hypertensive men. Comparative mean values from the study by Littler et al.*[8] *have been included*

					Precoital levels		*Peak coital levels*	
Case No.	*Age*	*Diagnosis*	*Episodes of sexual intercourse*	*Clinic BP (mmHg)*	*Heart rate (bt/min)*	*BP (mmHg)*	*Heart rate (bt/min)*	*BP (mmHg)*
2	42	Essential hypertension and coital cephalgia	1 (mistress)	165/115	80	150/90	120	218/120
			2 (wife)		68	135/86	123	243/151
			3 (mistress)		90	167/84	114	222/119
			4 (mistress)		65	128/67	125	233/133
			5 (mistress)		65	122/62	110	200/92
3	49	Hypertension with LVH	1	204/123	76	200/108	115	300/175
4	47	Essential hypertension	1	155/108	84	147/96	120	208/138
6	43	Essential hypertension	1	150/100	94	145/80	170	260/150
7	29		1	153/98	100	141/82	106	184/112
		Essential hypertension	2		80	150/97	110	213/136
		Treated hypertension	*3*	*140/85*	*105*	*125/68*	*120*	*206/120*
8	31	Essential hypertension	1	159/95	88	120/64	120	220/136
9	56	Essential hypertension	1	180/108	85	195/108	114	235/140
11	54	Essential hypertension	1	190/110	115	208/120	145	294/170
			2		100	162/82	142	286/160
Mean values	44		14 total	170/107	85	155/87	124	237/138
Littler *et al.*[8]	Mean 28	Normal subjects	6 total	128/78	78	120/80	131	185-115
n = 6								
Range	20–35			110–138/ 60–90	73-94	98–128/ 52–91	100-160	153–133/ 91–135

LVH, left ventricular hypertrophy.

Table 2 *Details of patients and coital blood pressure levels in three hypertensive women. Comparative values from the one case reported by Littler et al.*[8] *have been included*

					Precoital levels		*Peak coital levels*	
Case No.	*Age*	*Diagnosis*	*Episodes of sexual intercourse*	*Clinic BP (mmHg)*	*Heart rate (bt/min)*	*BP (mmHg)*	*Heart rate (bt/min)*	*BP (mmHg)*
1	41	Essential hypertension	1 ? orgasm	160/105	74	142/62	132	198/116
5	36	Essential hypertension, coital syncope	1 No orgasm	140/102	100	130/72	125	190/110
10	35	Essential hypertension	1 Orgasm	173/102	95	160/95	160	260/155
Mean			3 Total	158/103	90	144/76	139	216/127
Littler *et al.*[8]	37	Normal subject	1 No orgasm	130/ 85	66	98/52	96	120/75

course.[15–17] Though symptoms may be severe, such that invasive investigations have been performed, diagnoses of the underlying mechanism have remained speculative and treatment empirical. Lance[17] in his series describes raised resting blood pressure in seven of his 21 patients, in common with case 2.

Coital syncope was described in several of the patients reported by Kriz,[13] and tentative explanations have included hyperventilation, cardiac arrhythmia, hypotension, and cerebrovascular insufficiency caused by cervical spondylosis. In our patient the symptoms were clearly not those of *le petit mort,* occasionally described in association with profound orgasm, as some episodes were not associated with sexual activity. The normal results of investigations, lack of objective observers, and subsequent description of attacks, however, have led us to entertain a functional rather than organic diagnosis. In spite of the negative results in both these patients, ambulatory blood pressure monitoring did help to exclude some diagnoses and we feel its use should be considered in other similar cases.

The treatment of symptoms (and the prophylaxis against pathological events) associated with coitus could comprise any of a range of measures from complete abstinence to behaviour modification[18] and drug treatment. Jackson[19] reported that appropriate management in timing and conditions of coitus together with appropriate drug treatment could reduce considerably the incidence of anginal attacks, while Fox[20] showed that in one pair of (normotensive) subjects, propranolol reduced peak coital systolic pressure. Again in this respect (case 7), variability in response possibly defeated any attempt to show a definite trend (or lack of it) after beta-blockade. It may be that if isometric exercise is a prominent component of coitus the antihypertensive effect of beta-blockers and many other drugs may be limited,[21] though recent work in rabbits has shown reduction of peak coital heart rate, blood pressure, and plasma noradrenaline concentration after propranolol.[22]

The acquisition of further comparable information is clearly desirable, though the ethical objections to collecting data with invasive techniques are considerable and the reliability of non-invasive techniques of measuring blood pressure, especially during physical activity, is questionable. The elucidation of some recurrent symptomatic problems or evidence of their benign nature, however, may usefully be gained by this method.

We wish to thank Mr S Dashwood for technical help, and Drs P Taggart and A A Buchanan for permission to report cases under their care.

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Pyrophosphate heart scan in patients with progressive systemic sclerosis

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SUMMARY Scintigraphic examination of the myocardium, using ^{99m}Tc-labelled pyrophosphate, was carried out in 17 patients suffering from systemic sclerosis. This connective tissue disorder very often affects the myocardium secondarily. The results of the cardiac scan were compared with the information obtained from the electrocardiogram of systolic time intervals. In addition, spirometry was undertaken to detect a potential relation between cardiac and pulmonary involvement. The scan was found to be positive in seven patients and electrocardiographic findings were pathological in five patients only. The systolic time intervals were abnormal in three patients only. A ventilation disturbance was recorded in 10 patients. No clear relation was found between the results of the individual examinations. It is concluded that pyrophosphate heart scintigraphy may detect myocardial impairment in some cases of systemic sclerosis before it is manifested by heart failure. Examination of systolic time intervals is of little importance.

Scintigraphic myocardial imaging using ^{99m}Tc-labelled pyrophosate has recently become a standard procedure in some hospitals. This diagnostic method has proved useful especially in the detection of acute myocardial infarction.[1] The accumulation of the radiopharmaceutical in heart tissue, however, is not specific for fresh necrosis. Positive scintigraphic findings have been reported in a number of other heart diseases.[2–5] Hitherto, there has been very little experience with pyrophosphate heart scanning in cardiomyopathies. Only a few papers concerning this have been published to date, with conflicting results.[6–8] The introduction of new diagnostic methods in cardiomyopathies is important, as the recognition of these using present techniques is often difficult. Our group, therefore, has studied pyrophosphate cardiac scanning in various cardiomyopathies.

The results obtained from 17 patients suffering from progressive systemic sclerosis are presented. It is well known that diffuse scarring of the myocardium is a late finding in patients with this disease. This change leads to low cardiac output and death resulting from sudden arrhythmias or congestive heart failure.[9] The results of the pyrophosphate heart scan were compared with the findings obtained from a study of systolic time intervals. As progressive pulmonary fibrosis, with obliteration of the pulmonary capillary bed, may occur, and often leads to pulmonary hypertension and cor pulmonale, ventilation disturbances were also sought.

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Subjects and methods

Our series consisted of 17 patients in whom progressive systemic sclerosis was diagnosed using histological examination of a sample of affected skin. There were 13 female and four male patients aged from 20 to 77 years, average 52 years. All patients underwent physical examination; temperature was measured and urine and blood were routinely tested.

Scintigraphic examination was carried out using a Pho/Gamma HP scintillation camera (Nuclear Chicago) with a high resolution collimator. During scintigraphic observation anteroposterior, left anterior oblique, and left lateral projections were used. Two hours before the start of the scintigraphic observation, ^{99m}Tc-labelled pyrophosphate (370 MBq/10 mCi) was given intravenously. An analogue image was obtained by recording 200 000 to 300 000 counts on a film of Polaroid type. The digital image was obtained by recording the data on a CDS 4096 channel analyser. The intensity of the ^{99m}Tc-pyrophosphate uptake was graded from 0 to 4+ according to the method of Parkey *et al.*[10]

Heart rate, the total duration of systole, pre-ejection as well as ejection phases, mechanical systole, and QT interval were obtained. The quotient was calculated using the formula: pre-ejection phase divided by ejection phase. The systolic time intervals were obtained from a simultaneous electrocardiogram (lead II), phonocardiogram, and carotid pulse trace on a direct writing EK 21 Hellige multiscriptor. The paper speed was 50 mm/s. Systole was measured from the Q-wave on the electrocardiogram to the second sound on the phonocardiogram. The ejection phase was determined as the distance from the upstroke of the carotid pulse to the lowest point in its incisura. The pre-ejection phase was calculated as the difference between total systole and ejection phase. Patients were studied, fasting, always at the same time in the morning. After one hour's rest in a lying position the measurements were taken and a mean of 10 cardiac contractions calculated. To eliminate the influence of rate the values obtained were correlated using Weissler's indices. The results of the systolic time interval examination were summarised and labelled as "normal" or "pathological".

All patients were examined spirometrically. The vital capacity, timed expiration curve, and percentage vital capacity in the first second were measured. We also determined whether the ventilation of the lungs was normal or whether an obstructive, restrictive, or mixed ventilation disturbance was involved.

Results

The results are summarised in Table 1. It can be seen that the most frequent positive finding in the examination of the heart was that found on the myocardial scan. A pathological scan was recorded in seven patients; in 10 the scintigraphic image was normal.

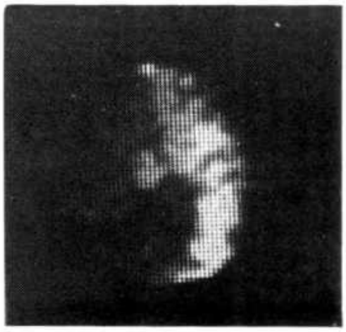

Fig. 1 *Pyrophosphate myocardial scan of case 7 with systemic scleroderma. Focal pathological activity 2+. Left lateral projection.*

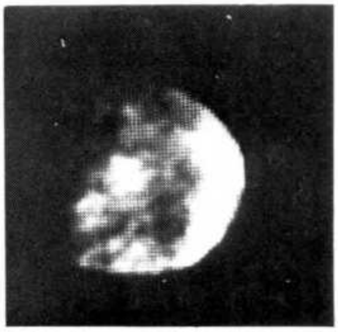

Fig. 2 *Pyrophosphate myocardial scan of case 4 with systemic scleroderma. Diffuse pathological activity 3+. Left lateral projection.*

Table 1 *Results of pyrophosphate heart scan, electrocardiogram, systolic time intervals, and spirometry*

Case No.	*Sex*	*Age*	*Scan*	*Electrocardiogram*	*STI*	*Abnormality of Ventilation*
1	F	63	Normal	Ventricular extrasystoles	Normal	Mixed
2	F	71	Normal	Normal	Normal	Normal
3	M	68	Normal	Normal	Normal	Normal
4	M	64	3+ diffuse	Normal	Normal	Restrictive
5	F	57	Normal	Normal	Normal	Normal
6	F	46	Normal	Incomplete right bundle-branch block	Normal	Normal
7	F	72	2+ focal	Normal	Normal	Mixed
8	F	54	Normal	Atrial extrasystoles	Normal	Mixed
9	F	49	2+ diffuse	Ventricular extrasystole inversion T in V_1–V_4	Pathological	Mixed
10	M	25	Normal	Normal	Pathological	Mixed
11	F	38	2+ focal	Normal	Normal	Normal
12	F	39	2+ focal	Normal	Normal	Mixed
13	F	56	Normal	Normal	Pathological	Mixed
14	M	20	Normal	Complete right bundle-branch block	Normal	Restrictive
15	F	77	3+ focal	Normal	Normal	Mixed
16	F	50	Normal	Normal	Normal	Normal
17	F	33	2+ focal	Normal	Normal	Normal

STI, systolic time intervals.

The focus of increased activity was 3+ (diffuse) in case 4 and 2+ (circumscribed) in cases 7, 9, 11, and 12 (Table 1). Examples of positive scintigraphic findings can be seen in Fig. 1 and 2. The electrocardiogram disclosed pathological findings in five patients, but these were not specific. In 12 cases the electrocardiogram was normal. Systolic time intervals contributed least; only three positive results were recorded, and in 14 cases results were normal. Spirometry showed a disturbance of ventilation in 10 patients, which was either of a mixed or restrictive type. The number of positive and negative findings in all examinations carried out is compared in Table 2.

Table 2 *Comparison of number of positive and negative findings*

	Positive	*Negative*
Scan	7 (41%)	10 (59%)
Electrocardiogram	5 (29%)	12 (71%)
Systolic time intervals	3 (18%)	14 (82%)
Spirometry	10 (59%)	7 (41%)

A mutual comparison of positive findings in individuals is more important that their absolute numbers. All four examinations yielded a positive result in one woman only (case 9). In nine patients at least two examinations were positive. Most frequently the results of the scan and spirometry concurred, both examinations yielding positive results in four patients. Electrocardiography and spirometry showed positive findings in three patients. Agreement between systolic time intervals and spirometry was seen in two cases. There was no agreement between the scan and the electrocardiogram or between the scan and systolic time intervals in any patient. In summary, each of the methods of study yielded some positive findings, but there was no clear relation between them.

Discussion

The interpretation of the findings is difficult. Necropsy or biopsy of the myocardium was not carried out in any patients, so we do not know how many had myocardial involvement by scleroderma. Nevertheless, it can be assumed on the basis of the results that, if a positive scintigraphic pyrophosphate scan is found, involvement of the heart in scleroderma can be presumed in patients where this is not clinically evident. In patients with heart failure such studies add nothing, because the involvement of the heart is already evident. Systolic time intervals seem of little help. Unfortunately, echocardiography could not be carried out; a comparison of this with the scintigraphic and electrocardiographic findings would be interesting. Spirometry, indicating possible involvement of the lungs, did not correlate closely with the cardiac results and is no guide to cardiac involvement; unfortunately we did not measure the diffusing capacity of these patients. Thus, of all these, only the pyrophosphate scan and the electrocardiography proved useful in the early detection of cardiac involvement in scleroderma. In this context the discrepancy between the two is surprising.

The interpretation of scintigraphic findings is difficult because we do not know enough about the behaviour of ^{99m}Tc-labelled pyrophosphate in damaged myocardium. According to current thinking, the pyrophosphate accumulates in the damaged cardiac muscle if the following three conditions are fulfilled[11]: (1) at least some fresh necrotic tissue must be present; (2) the blood flow through the region affected must be partially preserved; and (3) intramitochondrial calcium phosphate inclusions must be present. A bond of the radiopharmaceutical to these inclusions is assumed. Other authors, however, do not agree with the above hypothesis and assume a bond of the radiopharmaceutical to denatured proteins of damaged myocardial cells.[12] The fact that positive scintigraphic findings occur in fresh lesions only is of fundamental importance. This implies that myocardial involvement in scleroderma can be diagnosed by scintigraphy only while the disease is active, but not retrospectively. This could account for the discrepancy between the electrocardiographic and scintigraphic findings in our patients. Of course, all this is based on theoretical studies dealing with acute myocardial infarction, not with cardiomyopathies, but we believe these observations on the pyrophosphate cardiac scan in scleroderma to be original.

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Case reports

Br Heart J 1982; 47: 94–7

Malignant neurilemmoma of left atrium

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SUMMARY A 31-year-old woman, whose chief complaint was back pain, was found to have an echocardiographic abnormality suggestive of a left atrial myxoma. Angiography clearly showed a large radiolucent mass protruding from the left atrium into the left ventricle during diastole. *X*-rays of the sacrum disclosed the presence of a malignant tumour. Biopsy specimens taken from the tumour in the sacral plexus showed a malignant neurilemmoma. Despite extensive chemotherapy, widespread metastases developed and the patient died four months after admission. Necropsy disclosed three discrete tumours in the left atrium, which were found to be malignant neurilemmoma, shown on histology to be metastases from the primary in the sacral plexus.

Cardiac tumours, primary or secondary, are rare and their diagnosis during life is unfortunately difficult. Recently, however, echocardiography, especially M-mode and cross-sectional in combination, has proved valuable in this respect. The case presented in this paper is of special interest in that a neurilemmoma originating in the sacral region was complicated by three large secondary deposits in the left atrium, and precise diagnosis of the cardiac tumours was successfully made by echocardiographic techniques.

Case report

A 31-year-old woman remained in good health until the beginning of February 1979, when she noticed slight back pain and numbness in the left leg. These symptoms progressed rapidly and in April 1979, she was admitted with a suspected lumbar disc herniation. There was no history of syncope or of a heart murmur having been discovered. No embolic phenomema had occurred.

On examination, the blood pressure was 96/48 mmHg and the pulse rate was 98 per minute and regular. The first heart sound was loud, there was a grade 2/6 presystolic rumble best heard at the apex, and an early diastolic sound at the left sternal border in the fourth intercostal space, which closely resembled a mitral opening snap.

The lungs were clear. The haemoglobin was 10·4 g/10 ml, and the white blood cell count was 9400/mm.[3] The erythrocyte sedimentation rate was 105 mm/h. Serum potassium was 5.1 mmol/1, alkaline phosphatase 4·5 international units, and lactic dehydrogenase 628 international units/1. The electrocardiogram showed sinus rhythm, right axis deviation, a deep S wave in the left praecardial leads suggesting right ventricular hypertrophy, and right atrial enlargement. The chest *x*-ray film disclosed a normal configuration of the cardiac shadow and faint oval shadows in the left upper and right middle lung fields. An M-mode echocardiogram showed a mass of echoes appearing behind the anterior mitral leaflet during diastole, highly suggestive, but not absolutely diagnostic, of a left atrial tumour. On cross-sectional echocardiography, however, a left atrial tumour could be more clearly seen (Fig. 1). Angiography disclosed a large radiolucent mass which protruded from the left atrium into the left ventricle during ventricular diastole (Fig.2). A left atrial myxoma was diagnosed, the early diastolic sound being considered to be a tumour plop, but *x*-rays of the sacrum disclosed a destructive lesion at the left side of the sacrum,

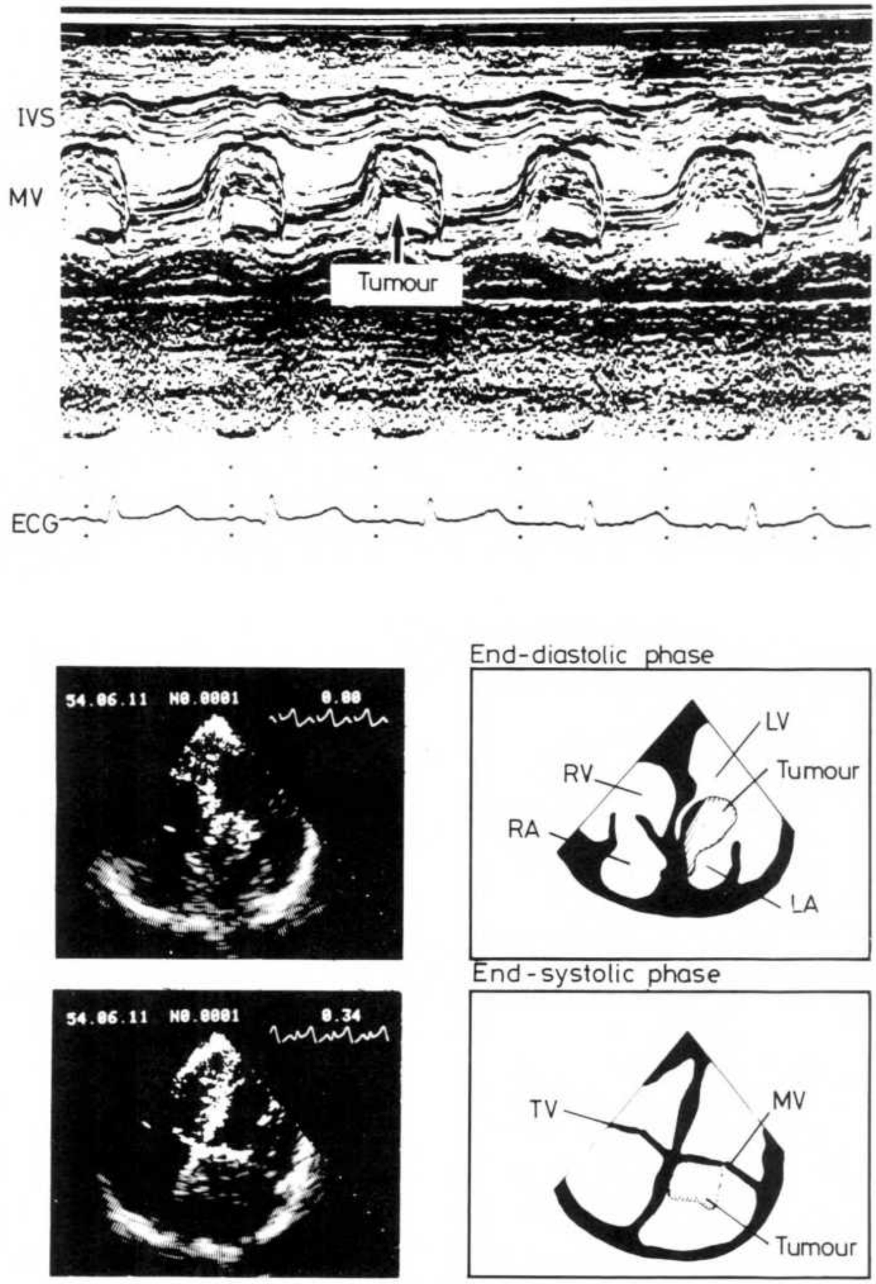

Fig. 1 *M-mode (upper panel) and cross-sectional (lower panels) echocardiograms (four-chamber views). M-mode echocardiogram shows a mass of echoes appearing behind the anterior mitral leaflet during diastole. Cross-section echocardiogram shows a left atrial mass. IVS, interventricular septum; RV, right ventricle; RA, right antrium; LV, left ventricle; LA, left atrium; TV, tricuspid valve; MV, mitral valve.*

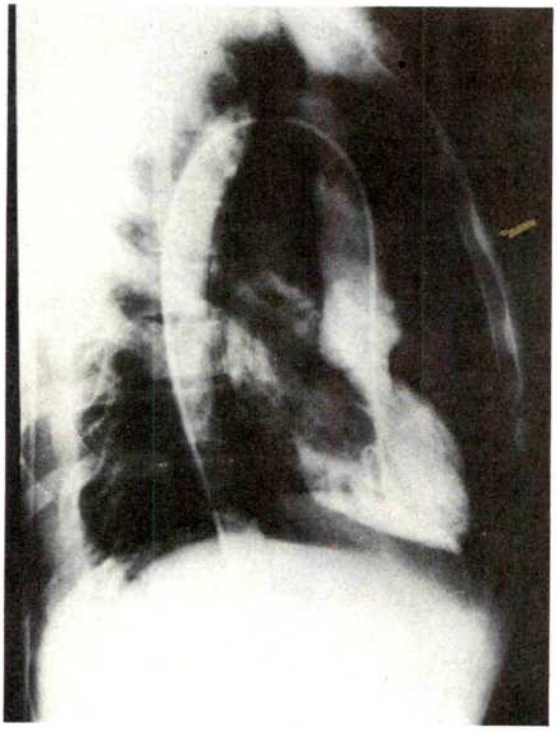

Fig. 2 *Left ventricular angiography showing a radiolucent mass protruding from the left atrium into the left ventricle during diastole. This finding is suggestive of the presence of a mobile left atrial mass.*

indicating the presence of a malignant tumour, and biopsies from a tumour in the sacral plexus showed it to be a malignant neurilemmoma. This was not considered resectable. The patient was subsequently treated by chemotherapy, but there was no response. Widespread metastases developed and she died four months after admission.

POSTMORTEM FINDINGS

The pericardium was normal and there were no pericardial adhesions or significant fluid. The heart was slightly enlarged, weighing 300 g. The thickness of the right ventricular free wall was 3 mm. Upon opening the left atrium, three myxoid fibrous tumour masses were found (Fig. 3A). The largest one, measuring 45 × 35 × 30 mm, ovoid in shape, protruded from the atrial septum on a short pedicle. The other two tumour masses, both of which were located in the anterior commissural region of the mitral valve, measured 30 × 25 × 20 mm and 30 × 20 × 20 mm, respectively. They were elastic, firm, fibrous but partly myxoid with whorled patterns. In the retroperitoneal space, there was a huge tumour mass, 13 × 10 × 10 cm, covered by a thin fibrous capsule. On cut section, the tumour was firm and fibrous, with haemorrhagic and necrotic areas. There were multiple metastases elsewhere, many scattered in the lungs.

HISTOLOGICAL FINDINGS

The histological findings of the tumours in the left atrium were identical to those of the primary in the retroperitoneal space. They were highly cellular and composed of plump spindle cells with ovoid or spindle-shaped nuclei. The spindle cells were arranged in wavy fascicles, simulating the Schwann cell cords. The nuclei were arranged in a parallel fashion, forming a striking palisade pattern (Fig. 3a and c) with some aberrant cells showing bizarre mitotic activity. These findings suggested a malignant neurilemmoma (Schwannoma) primarily arising from the left sciatic nerve.

Discussion

Malignant neurilemmoma is a malignant neoplasm, arising in the perineurium of large nerves, characterised by the morphological patterns of Schwann cell differentiation. Neurilemmoma of the heart has been reported before,[1-5] but its occurrence in the left atrium is extremely rare. In this case the primary retroperitoneal tumour arose in the sacral plexus and metastasised to the left atrium after passing through the pulmonary circulation, both the cardiac and the sacral tumours showing the typical naked eye and cytological pattern of a neurilemmoma. The retroperitoneal tumour was far larger than the left atrial tumours, and the latter arose from the endocardium without invasion of the underlying myocardium. This indicates that the retroperitoneal tumour was the primary and the cardiac lesions were metastatic deposits resulting from endocardial implantation of tumour emboli. This mechanism was considered by Crofts and Forbes[2] to be the explanation for a left atrial secondary deposit in their case of malignant neurilemmoma of the lung. The alternative, in our case, that the tumours were all separate primaries which grew simultaneously and independently is unlikely, for then the cardiac tumours would have originated from the cardiac plexus and would have occurred in the myocardium or on the external aspect of the base of the heart, not within the atrium.

The combined use of M-mode and cross-sectional echocardiography clearly identified the presence of left atrial tumours in our patient but was not able to distinguish the pathological causes. The case appears to be unique.

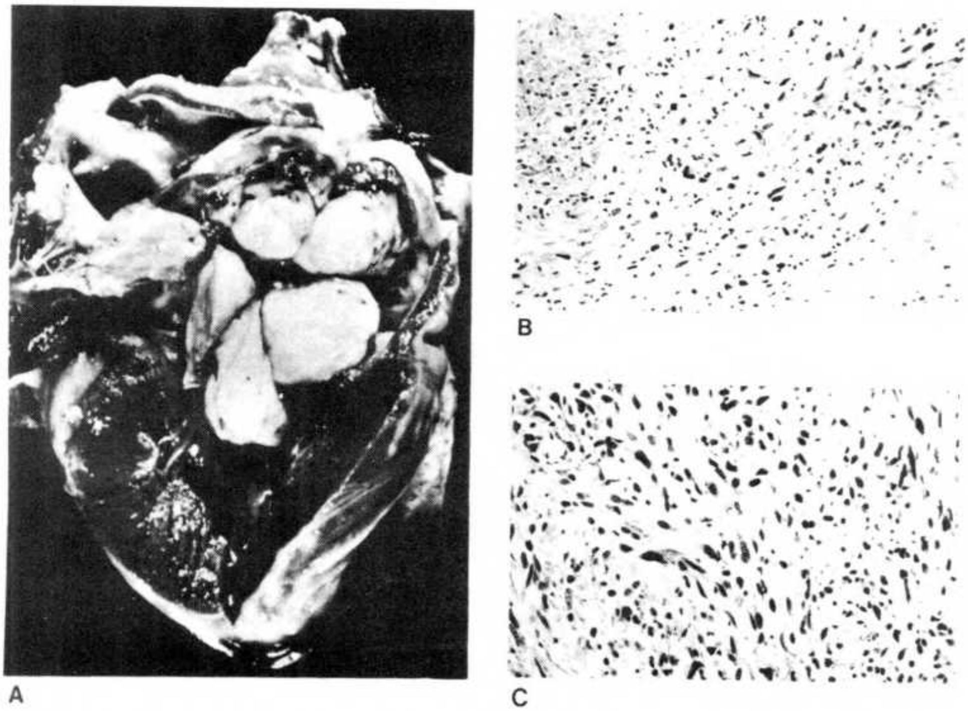

Fig. 3 *(A) On opening the heart, three tumour masses are found occupying the left atrium, one of which protrudes from the atrial septum on a short pedicle; the other two bulge from the anterior commissure of the mitral valve like a dumb-bell. (B) The tumour in the left atrium. (H and E. stain. Original magnification × 100.) (C) The tumour in the retroperitoneal space. (H and E stain. Original magnification × 200.) The tumour cells are spindle or ovoid, with wavy fibre formation. Their nuclei are hyperchromatic, varying in size and shape, with giant cell formation in places.*

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Br Heart J 1982; 47: 98–100

Pacemaker-masked hypertension in a patient with mitral stenosis

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SUMMARY Severe hypertension was seen in a patient with mitral stenosis when in sinus rhythm. A large fall in systolic blood pressure and in left ventricular end-diastolic pressure was caused by ventricular pacing. Contrary to the usual situation in mitral stenosis this patient paradoxically is a subject who improved haemodynamically with the loss of sinus rhythm and of atrial systole.

Permanent endocardial pacing systems have an established place in the treatment of conduction system disease. Until recently ventricular pacing was the established norm but there are increasing reports that a more "physiological" form of pacing may further enhance cardiac performance. These new systems preserve atrial systole by sequential atrial and ventricular pacing.[1] Inevitably such systems are being inserted in patients who have concomitant valvular heart disease. There seems little doubt that physiological pacing greatly improves the haemodynamic performance in aortic stenosis.[2 3] In mitral stenosis the contribution of atrial systole to cardiac performance is still controversial. About half the published series claims that loss of atrial systole is unimportant.[3 4] Others have found the opposite.[2 5 6] This report describes a patient with mitral stenosis in whom ventricular pacing and loss of effective atrial systole lowered peak left ventricular pressure to such an extent that severe concomitant essential hypertension was masked.

Case report

The patient was a 70-year-old woman who had rheumatic fever in 1918 and has been known to have had rheumatic heart disease since her mid-40's. In 1976 she had a syncopal episode and was diagnosed as having sick sinus syndrome. At least one asystolic episode lasting five seconds was noted during the course of 24-hour electrocardiographic monitoring. As a result she had an ELA lithium pacemaker inserted in November 1976. She has had frequent follow-up visits to both the cardiac clinic and the pacemaker clinic and during these visits her blood pressure has been noted to vary from 270/120 to 160/90 mmHg. She had been variably treated with methyldopa and oxprenolol but at the time of subsequent cardiac catheterisation she was on frusemide (40 mg mane), Slow K, digoxin, warfarin and disopyramide.

Her history was of breathlessness on exertion. This was very variable as some days she could walk for three miles on the flat and manage stairs reasonably well while on other occasions this made her very breathless.

On physical examination she looked fit and there was no evidence of cardiac failure. Her heart rate was 71 a minute. Blood pressure supine was 160/90 mmHg. The apex beat was left ventricular in type and displaced outwards and downwards. Clinically she had the signs of moderately severe mitral stenosis with only minimal aortic and mitral regurgitation.

Chest *x*-ray film showed moderate cardiomegaly with some unfolding of the aorta. Her electrocardiogram, in sinus rhythm, showed left ventricular strain pattern. Echocardiography confirmed the presence of moderately severe mitral stenosis. At cardiac catheterisation pulmonary artery pressure was around 40 mmHg systolic and she had a mean mitral valve gradient of 7 to 8 mmHg. Aortic pressure was 160/90 mmHg while left ventricular pressure was 160/0 to 10 mmHg. These pressures were obtained during pacing rhythm. While the catheter was in the left ventricle the patient's own sinus rhythm inhibited the pacemaker. There was an immediate rise in the left ventricular peak pressure and also in end-diastolic pressure (see Fig.). Within 30 seconds this rise was of the order of 100 mmHg, with left ventricular pressure reaching a value of 260/20 to 30 mmHg. There was no aortic gradient. Left ventricular angiography showed only trivial mitral regurgitation while an aortogram showed mild aortic regurgitation only. Selec-

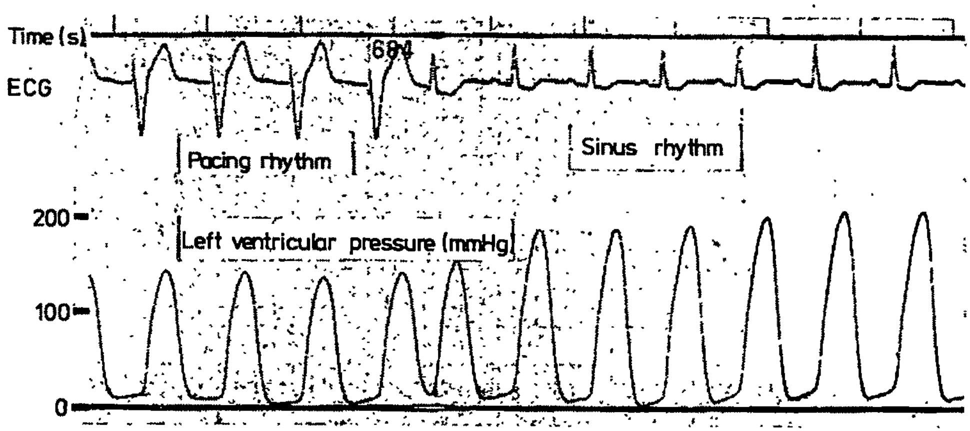

Fig. *Simultaneous left ventricular pressure trace and electrocardiogram. When the patient's own sinus rhythm inhibits the pacemaker there is an immediate increase in both left ventricular peak and end-diastolic pressures.*

tive coronary arteriograms showed these vessels to be natural and free from disease.

Discussion

Harvey, in 1628, noted that when the ventricle of the frog was cut open fluid spurted from it in time with contraction of the atria. The active part played by atrial systole in ventricular filling has been controversial ever since. When such factors as heart rate, PR interval, and ventricular diastolic volume are taken into account, however, there seems little doubt that atrial systole contributes around 10 to 20% of left ventricular output in normal hearts.[7]

In mitral stenosis the diastolic gradient increases with atrial systole and so does the diastolic flow across the valve. Thus, factors such as heart rate (and therefore duration of diastole) and severity of stenosis will determine the contribution of atrial systole to left ventricular filling. In severe mitral stenosis atrial systole will be needed to force blood through the valve and to increase ventricular end-diastolic volume and hence cardiac output.

The loss of sinus rhythm in mitral stenosis generally leads to haemodynamic deterioration. The fibrillating atria no longer contract effectively, thus reducing the diastolic gradient over the valve and hence diastolic flow while the rapid heart rate and shortened diastole further reduce diastolic ventricular filling. In our patient paradoxically the loss of sinus rhythm seemed to have beneficial haemodynamic effects. While pacing the blood pressure was normal as was her left ventricular end-diastolic pressure. With pacemaker inhibition and the return of sinus rhythm, end-diastolic pressure trebled and systolic blood pressure increased by up to 100 mmHg and she was clearly hypertensive. The haemodynamic changes seen with pacing were likely to be sustained as the patient was seen on many occasions at the clinic when she was in pacing rhythm and her blood pressure was normal.

It is interesting to speculate upon the mechanism of the raised end-diastolic pressure which was presumably the reason why some days the exercise tolerance was substantially better than others. It seems that a combination of increased preload (right atrial systole increasing right ventricular output and left atrial pressure) and increased afterload both contribute (left atrial systole increasing diastolic flow into the left ventricle, and cardiac output increasing into what was presumably a cardiovascular system with a relatively increased and fixed resistance). Support for this comes from Chamberlain *et al.*,[1] who showed that sequential atrioventricular pacing in patients with heart disease (admittedly not involving the valves) resulted in a fall in central venous pressure and a rise in systemic blood pressure.

In our patient it is also possible that paced beats were less efficient and that the paced ventricle could not generate the power to raise the blood pressure. It has been shown that the left ventricle produces less stroke work for a given end-diastolic pressure during ventricular pacing[8] and that the rate of ventricular contraction is reduced. Diastole is also thus shortened, with presumably a consequent fall in flow across the valve especially if the valve is stenosed.

In any event though both the pacing and sinus heart rates were virtually identical (see Fig.) the circulatory status of the patient changed conspicuously for the better with the loss of atrial systole, thus supporting the view that atrial systole does have haemodynamic significance in mitral stenosis. In this particular patient it was of such a magnitude that severe systemic hypertension was masked when atrial systole was lost.

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Br Heart J 1982; 47: 101–2

Penicilin-sensitive *Moraxella* prosthetic endocarditis

Near disaster caused by failure to treat with penicillin

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SUMMARY A patient with late prosthetic endocarditis resulting from *Moraxella non-liquefaciens* is reported. Correct laboratory indentification is of therapeutic importance as *Moraxella* is often highly sensitive to penicillin. Because of suspected penicillin sensitivity, antibiotics other than penicillin were used, but failed to control the endocarditis. Prompt response occurred when penicillin was given. Penicillin remains by far the most effective antibiotic for the treatment of endocarditis, particularly when affecting prosthetic valves, and caused by organisms sensitive to penicillin.

Penicillin remains the most effective antibiotic in the treatment of infective endocarditis caused by organisms sensitive to penicillin. In this case report, the near disaster caused by withholding penicillin and the prompt response to penicillin is described in a patient with late prosthetic valve endocarditis caused by *Moraxella non-liquefaciens*.

Case report

A 32-year-old housewife was admitted to the University Medical Unit, Queen Mary Hospital, in February 1980. She had rheumatic mitral stenosis, mitral regurgitation, and aortic regurgitation diagnosed in 1960. Skin test for penicillin sensitivity using intradermal injection of penicillin was positive, with the formation of a large wheal measuring 5 cm in diameter. It was considered that the patient was sensitive to penicillin, and sulphadiazine was given for prophylaxis. In November 1972, she underwent double valve replacement. A Björk-Shiley valve was inserted in the mitral position and a Starr-Edwards valve (model 1260) in the aortic position. In February 1980 she was admitted because of pyrexia, chills, and rigor. Examination showed a temperature of 39·1°C. There was no clubbing, Osler's node, petechiae, splinter haemorrhage, or mucosal haemorrhage. She was in atrial fibrillation with a ventricular rate of 100 per minute. Blood pressure was 120/80 mmHg. On auscultation of the heart, the prosthetic sounds were normal. There was a diastolic rumbling murmur at the apex and an ejection systolic murmur at the aortic area. The spleen tip was palpable. Fundal examination was normal. Investigations showed a haemoglobin level of 11·9 g/100 ml and a blood leucocyte count of 12 500 per mm^3, with 70% polymorphs. Erythrocyte sedimentation rate was 43 mm in the first hour. Urinalysis and renal function tests were normal. Electrocardiogram showed atrial fibrillation. Chest *x*-ray film showed cardiomegaly. Normal prosthetic valve movements were shown on fluoroscopy. Both M-mode and two dimensional echocardiograms failed to demonstrate vegetations. On the third hospital day, she was started on streptomycin 0·5 g intramuscularly every twelve hours and cephalothin 2 g intravenously every six hours. Six days later, the preliminary report of the blood cultures indicated growth of "*Alcaligenes species*", sensitive to ampicillin, carbenicillin, cephamandole, kanamycin, gentamicin, tetracycline, and co-trimoxazole. She still had a pyrexia ranging from 37·2°C to 38·3°C. Cultures of urine, sputum, faeces, and throat swab were negative. Repeated erythrocyte sedimentation rate was 92 mm in the first hour. There was microscopical haematuria. Rheumatoid factor and antinuclear factor were negative. C3 level was 130 mg/100 ml (normal 86 to 184 mg/100 ml) and C4 level 36 mg/100 ml (normal 24 to 80 mg/100 ml). Cephalothin and streptomycin were discontinued and she was given gentamicin 60 mg intramuscularly every eight hours. The fever still persisted after ten days of gentamicin, which was stopped on the 18th hospital day. The "*Alcaligenes species*" isolated from the blood was later identified to be *Moraxella non-liquefaciens* according to tests recommended by Cowan.[1] It was highly sensitive to penicillin, the minimal inhibitory and bactericidal concentrations being 0·25 and 1·0 units/ml, respectively. Penicillin was withheld in view of her previous history of suspected penicillin sensitivity. On the 27th hospital day, the temperature rose to 40°C and she was given cephamandole 1 g intravenously every six hours. As fever persisted, she was given penicillin by intravenous infusion, 10 megaunits daily. After two days the fever subsided. She remained afebrile and the soluble penicillin was continued for six weeks. On the 42nd hospital day she developed cerebral embolism resulting in transient left hemiparesis. When last seen four months after discharge, the spleen was not palpable and her erythrocyte sedimentation rate was 20 mm in the first hour.

Discussion

Our patient illustrates two important points. Firstly, moraxella is an unusual causative organism of infective endocarditis. It had been reported to affect natural valves.[2–4] We believe that our patient is the first reported case of prosthetic valve endocarditis caused by moraxella. Recognition of this is of clinical importance as moraxella is often highly sensitive to antibiotics,[5] whereas other Gram negative enteric bacteria, which moraxella may be mistaken for, are not. Secondly our patient shows that despite the discovery of numerous new potent antibiotics, penicillin remains the best antibiotic for treating infective endocarditis caused by penicillin-sensitive organisms. This should be used whenever possible. In our patient, other antibiotics were initially tried because of the positive skin test to penicillin. The test had been performed in 1960, when it was done routinely in our department in all patients before they received penicillin. This is no longer a practice because of the various limitations of the test.[6] None the less, aminoglycosides and cephalosporins were given initially as the *Moraxella non-liquefaciens* isolated was found to be sensitive to them. Despite the laboratory findings, however, these antibiotics failed to control the endocarditis. With the institution of penicillin, clinical response occurred promptly and complete cure resulted after treatment for six weeks. This was in pronounced contrast to the near disaster when other antibiotics were used, illustrating the importance of using penicillin, whenever possible, in treating infective endocarditis caused by penicillin-sensitive organisms.

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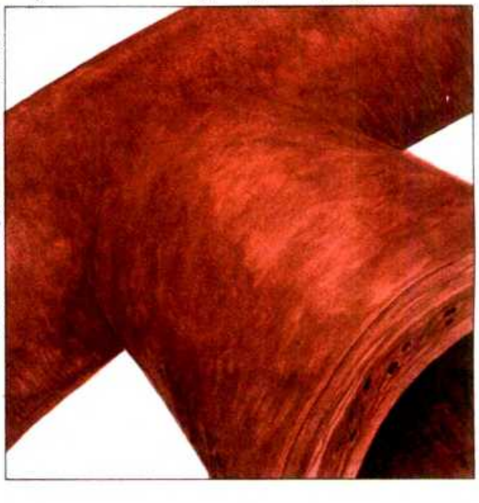

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Br Heart J 1982; 47: 103–5

Mycotic aneurysm at site of formerly ligated ductus arteriosus caused by infective endarteritis

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SUMMARY A mycotic aneurysm caused by infective endarteritis occurred at the site of a formerly ligated ductus arteriosus. Because of external pressure by the aneurysm upon the aorta, the clinical syndrome of coarctation of the aorta was mimicked. After antibiotic treatment successful surgery was performed.

The risk of developing infective endocarditis in relation to a pre-existing cardiac lesion varies according to the lesion. In persistent ductus arteriosus it is approximately one in every 300 patient-years. Assuming a 70 year life a patient with persistent ductus arteriosus has a 20% risk of developing infective endocarditis. After surgical closure it is presumed that this risk declines to that of a healthy individual[1] and that antibiotic prophylaxis can be omitted after the early postoperative period.[2 3] We describe a patient who developed a mycotic aneurysm of the descending aorta caused by infective endarteritis at the site of a persistent ductus arteriosus which had been ligated 11 years earlier.

Case report

A 12-year-old girl was admitted to hospital because of pyrexia, malaise, weight loss, and diffuse arthralgia of four weeks' duration. She had been treated with oral penicillin elsewhere for one week. A small membranous ventricular septal defect was known to be present and she had had a large persistent ductus arteriosus ligated at the age of 1 year. Cardiac recatheterisation at the age of 9 years had shown a pulmonary systemic flow ratio of 1·4:1, with a normal pulmonary artery pressure. Left ventricular angiography had shown the small defect in the membranous interventricular septum. The aorta was normal.

On admission, physical examination showed a pale, ill-looking girl, weighing 34·5 kg, with a body temperature of 39° C. There was pretibial oedema, slightly swollen painful ankle joints, and a non-specific erythema on the legs. The arm blood pressure was 145/95 mmHg bilaterally and the systolic blood pressure in the legs was 100 mmHg. The radial pulses were easily palpable, in contrast to the femoral pulses. The spleen was enlarged. In the fourth left intercostal space a grade 3/6 pansystolic murmur was heard and in the second left intercostal space there was a grade 2/6 ejection murmur, radiating to the back. There were no other abnormal findings, exept for the presence of some diseased teeth. Laboratory data on admission included the following: erythrocyte sedimentation rate 65 mm/hr, haemoglobin 10·6 g/100 ml, white blood cell count 11 000/mm^3, thrombocytes 357 000 mm^3, blood urea nitrogen 12·3 mmol/l (74 mg/100 ml), creatinine 300·6 mmol/l (3·4 mg/100 ml), gamma-globulin 20·1 mg/ml, total protein 8·0 g/100 ml. Examination of the urine disclosed proteinuria, leucocytes, and red cells, with some red cell casts.

The electrocardiogram was normal. On chest *x*-ray examination the heart was slightly enlarged to the left and the descending aorta showed a pronounced dilatation over a distance of about 5 cm. The echocardiogram was normal. An aneurysm of the descending aorta was suspected, possibly caused by infective endarteritis at the site of the previously ligated persistent ductus arteriosus. The signs of coarctation of the aorta, which were definitely new, were presumed to be caused by the aneurysm. It was felt she also had glomerulonephritis. After blood samples had been taken for anaerobic and aerobic cultures, antibiotic treatment was started immediately: 30 000 000 U penicillin G intravenously daily for six weeks, and 700 mg streptomycin intramuscularly daily for two weeks. All cultures proved to be sterile. In the first week of treatment the erythrocyte sedimentation rate gradually returned to normal, the arthralgias disappeared, body temperature became normal, and renal function improved.

Cardiac catheterisation was performed one week after the completion of treatment. The left ventricular angiogram again showed the small membranous ventricular septal defect. The aortogram showed an irregular aneurysm in front of and pressing on the descending aorta (Fig.).

At operation one week later the aneurysm was found to have its origin at the site of the formerly ligated persistent ductus arteriosus. There was no communication between the aorta and the pulmonary artery. The aneurysm extended downwards and compressed the aortic wall from the outside, narrowing the inner diameter of the aorta over a distance of 1 cm. In order to resect the aneurysm and the surrounding tissue the aorta had to be clamped proximally and distally, which required axillofemoral bypass. A "dacron" woven graft was inserted. On histological examination of the excised tissue a chronic inflammatory reaction was seen. Aerobic and anaerobic cultures of a tissue specimen remain sterile.

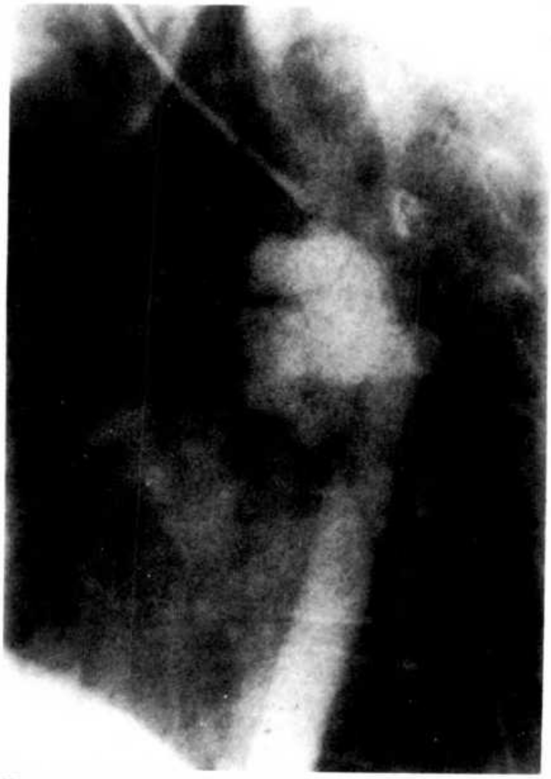

Fig. *Aortogram (left oblique view) showing an irregular aneurysm in front of and pressing on the descending aorta.*

Two years after operation the girl is well and her blood pressure is 110/70 mmHg.

Discussion

Surgical closure of the persistent ductus arteriosus has a very low mortality and is therefore advised even in a patient whose ductus carries a haemodynamically insignificant shunt to eliminate the relatively high risk of developing infective endocarditis.[4] Recanalisation or incomplete closure of a persistent ductus that has been only ligated occurs infrequently[5] and in such patients the risk of infective endocarditis remains high,[6] the site of infection being the usual one localised at the pulmonary end of the ductus.[7] In our patient the ligated ductus has been proved to be closed but a mycotic aneurysm had developed in the descending aorta at its former site. This suggests that this area remained an endocarditis prone lesion. More than 90% of mycotic aneurysms are the result of infective endocarditis, a complication produced by infected microemboli passing into the vasa vasorum. A minority of mycotic aneurysms originate in arteries at the site of previously injured endothelium by direct seeding of micro-organisms.[8] It might be argued that in our patient the aneurysm was secondary to endocarditis on the ventricular septal defect but in this condition the vegetations are generally localised on the right ventricular side of the septum or on the endocardium in the right ventricle opposite the defect,[7] and in the absence of right-to-left shunting, as was the case here, infected emboli from these areas are not very likely to enter the systemic circulation. Furthermore there were no signs of intracardiac vegetations on echocardiography. Thus, it is probable that the endocarditis in our patient was primarily the result of an endarteritis causing direct seeding of micro-organisms on previously injured endothelium at the site of the ligated ductus. The source of these micro-organisms could have been dental but unfortunately blood cultures remained sterile, possibly because penicillin had been given before admission.[9] The treatment we gave of penicillin in high dosage, in combination with streptomycin, was that indicated in patients with culture negative endocarditis.[10]

Resection of the aneurysm in our patient was performed after completion of antibiotic treatment. This is recommended,[11] but is not always successful, since persistence of the aortitis can occur despite adequate blood levels of antibiotics. Because of this and the risk of aneurysmal rupture immediate operation is possible[12] and will be preferred by us in future cases. This case illustrates that infective endocarditis can still occur after surgical closure of a persistent ductus arteriosus, even after 11 years. Such patients should be followed long term and it may not be as safe to omit antibiotic prophylaxis against bacterial endocarditis in them as is generally accepted.

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Br Heart J 1982; 47: 106

Invasive electrophysiological study in the Jervell and Lange-Nielsen syndrome

Sir,

In a recent case report (*Br Heart J* 1981; 45: 225–9) Hartzler and Osborn, recording bipolar right ventricular electrograms in a case of the Jervell-Lange-Nielsen syndrome, observed late and bizarre waveforms prolonging abnormally the repolarisation phase. They think that these alterations may represent "part of the 'T wave', or possibly the intracardiac counterpart of the 'U wave'." We can confirm this observation and also the hypothesis that these abnormal waveforms correspond to the U wave of the surface electrocardiogram. We recorded monophasic action potentials by suction electrocatheter in 10 cases of the long QT syndrome with severe ventricular arrhythmias, of which eight were acquired and two idiopathic: all showed asynchronous ventricular repolarisation.[1] Potentials recorded in different areas of the right ventricle showed large and pathological differences in duration (from 100 to 270 ms) and the longest showed obvious "humps" towards the end of repolarisation. When the "humps" were wide enough they were able to trigger focal re-excitation, that is, isolated ventricular extrasystoles and/or "torsades de pointe". These "humps" appear to correspond to pathological U waves on the surface electrocardiogram.[1–3] Our "humps" therefore correspond to the phenomena observed by Hartzler and Osborn but they are much more evident and thus their interpretation is much easier.

We agree that in doubtful cases of the long QT syndrome electrophysiological study is helpful but think that simultaneous monophasic action potential recordings are important.

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Correspondence

Br Heart J 1982; **47**: 107–8

Atresia of left atrioventricular orifice

Sir,

In their paper (*Br Heart J* 1981; **45**: 393–401) Thiene *et al.* state that in order to avoid confusion and discrepancies in nomenclature with regard to the terms "mitral" and "tricuspid" atresia they prefer to distinguish between atresia of left and right atrioventricular orifices. This implies that cardiac malformations of different pathogenesis are lumped together. If this is overlooked one might erroneously assume that natural entities are classified. Morphological characteristics and spatial relations inherent in the asymmetrical development of the morphological right and left side of the heart are neglected. The left to right asymmetry of the ventricular part of the heart, to which valve morphology is always secondary, is concealed by describing structures as left and right hand instead of as morphologically left and right.

It is not always easy to distinguish between the morphological left and right side of the heart, but quite a number of features can be used as guidance, for example the ventricular morphology, the position of the conducting system, the relation of the septum to the crux, and the position of a rudimentary chamber. The atretic left atrioventricular orifice may be either the mitral or the tricuspid orifice, dependent on the bulboventricular loop during cardiac development.

In our opinion the nomenclature now proposed by Thiene *et al.* unnecessarily simplifies terminology to such an extent that the material becomes less accessible to those who try to understand the developmental background of cardiac malformations. They simplify morphology itself, which cannot be done without causing confusion.

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Anatomisch-Embryologisch Laboratorium
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Netherlands.

This letter was shown to Dr Thiene and his co-authors who reply as follows:

Sir,

We must admit to being confused as to the precise problem encountered by Drs Gittenberger-de Groot and Wenink. We were at pains to point out in our introduction the problems inherent in the use of "mitral" and "tricuspid" atresia. We then emphasised that the hearts studied were unified by the fact that they had no direct communication between the morphologically left atrium and the ventricular mass. In terms of left atrial morphology the hearts then are very much a "natural entity", accepting that there is a difference between an imperforate valve and an absent connection (see below). Drs Gittenberger-de Groot and Wenink suggest that we describe structures as left and right hand rather than as morphologically left and right. Fig. 1 of our paper gave a clear account of all the hearts studied, describing how the morphologically right atrium was connected in some hearts to morphologically right ventricular chambers, and in other hearts to morphologically left ventricular chambers. This Figure also illustrated the important variation in relation of a rudimentary right ventricular chamber when the right atrium connected to a morphologically left ventricular chamber. We described the relation of a septum to the crux of the heart in all the hearts categorised as "univentricular". In other words, we described all the features they discuss in their second paragraph apart from the position of the conduction system. We also pointed out how in some hearts the atresia was the result of an imperforate valve membrane and in others the result of absence of the left atrioventricular connection.

We submit, therefore, that we described precisely the anatomy of the hearts studied. Drs Gittenberger-de Groot and Wenink apparently criticise us for not describing the presumed anatomy of a structure that is not there; that is the absent left atrioventricular connection. Our introduction and discussion were designed to show how the problems in nomenclature devolve from overemphasis upon embryology, this itself derived from presumptions concerning nonexistent structures. Apparently the Leiden workers wish to perpetuate this confusion. If so, then all the information they require to make their presumptions is clearly stated in our paper. We wished to remove such confusion and believe we have done so. We strongly contest their claim that we have simplified morphology. All we have done is to describe morphology as it is observed.

G Thiene,
R H Anderson, and
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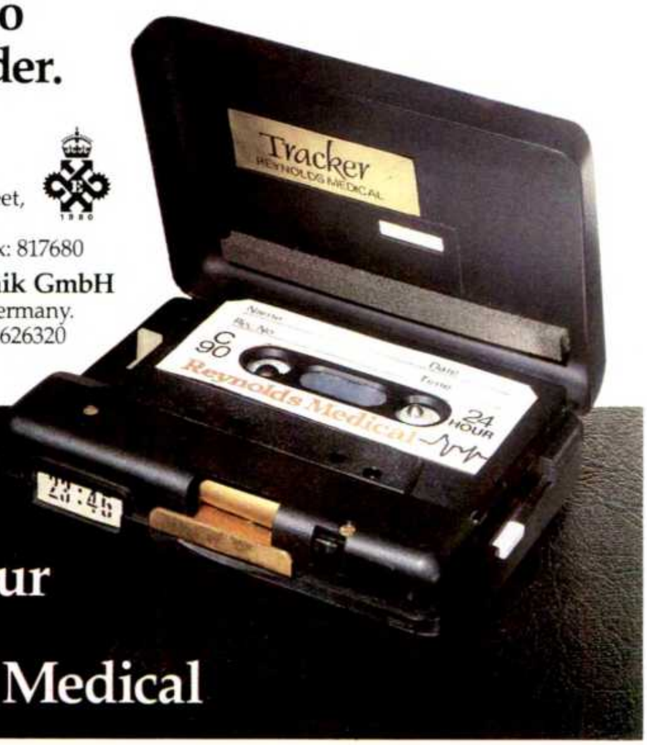

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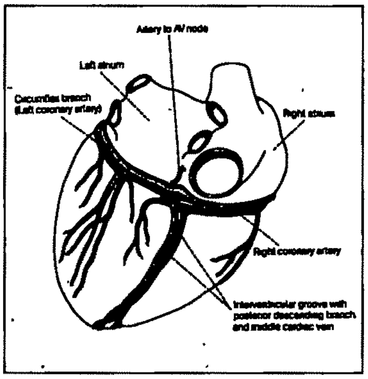
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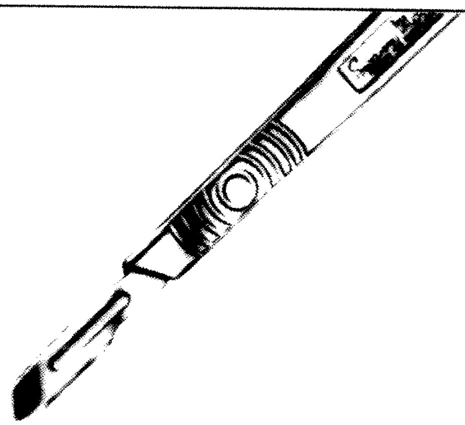

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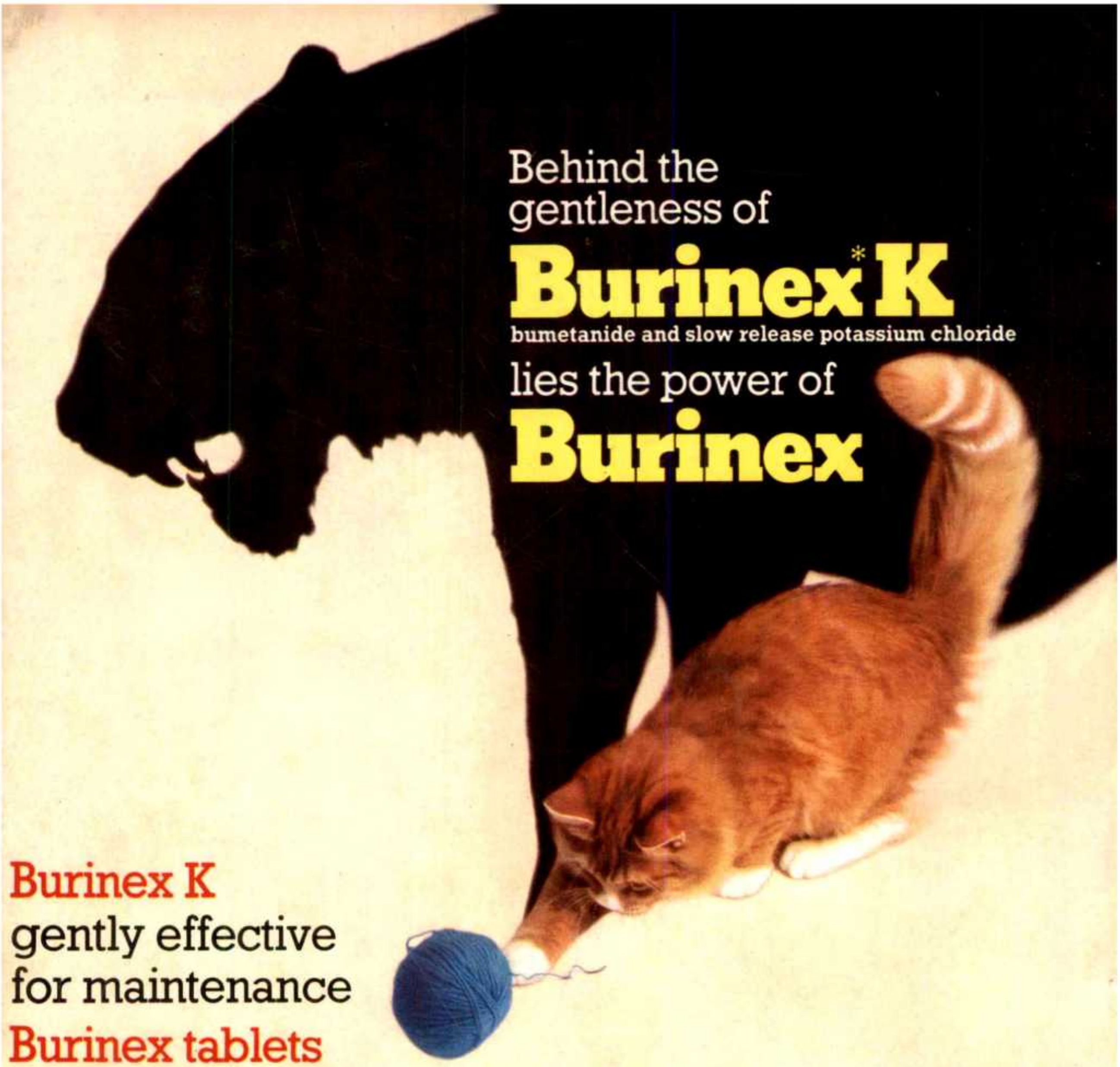

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Illustrations should be identified on the back with Figure number in Arabic numerals and name of author. Legends should be typed on a separate sheet of paper. Figures should be on glossy paper and unmounted unless several are grouped together as in montage. Lettering to be inserted should be indicated lightly in pencil on a transparent overlay. *Diagram, charts,* and *line drawings* should be drawn in indian ink. Only black-and-white *electrocardiograms* make satisfactory blocks, and photographs should be sent rather than original. If several electrocardiograms are grouped in a single Figure, only a few complexes should be shown, and the width should not exceed 14 cm unless a reduction in scale is feasible. *Radiographic prints* (see Editorial, vol 35, p 1101, 1975) should be submitted unmounted as facsimile (negative) glossy prints of at least half-plate size, with as long a tonal range as possible. Include only area under discussion. Letraset arrows, transparent overlays, and explanatory line drawings should be used when necessary. Identify on back with author's name, "TOP", and figure number written in felt tip pen.

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(1) *Standard journal article*—(List all authors when six or less; when seven or more, list only first three and add *et al.*):
  Walmsley R. Anatomy of left ventricular outflow tract. *Br Heart J* 1979; **41**: 263–7.

(2) *Books and other monographs:*
  Macartney FJ, Partridge JB, Shinebourne EA, Tynan MJ, Anderson RH. Identification of atrial situs. In: Anderson RH, Shinebourne EA, eds. *Paediatric cardiology 1977*. Edinburgh, London: Churchill Livingstone, 1978: 16-26.

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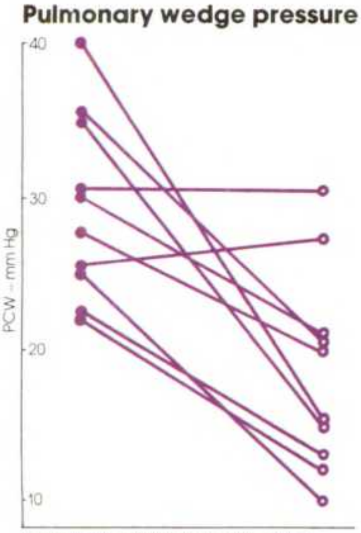
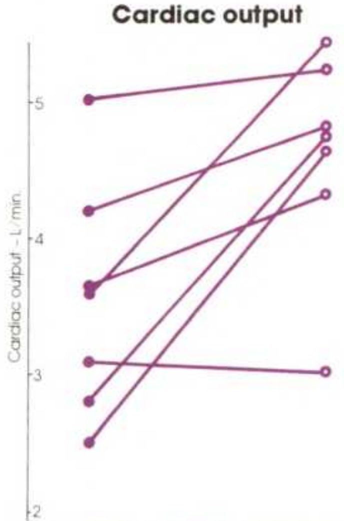
In moderate to severe heart failure unresponsive to digitalis and diuretics the goal of therapy is to reduce elevated pulmonary arterial and left ventricular end-diastolic pressures and increase cardiac output whilst minimizing any fall in arterial pressure.[1]

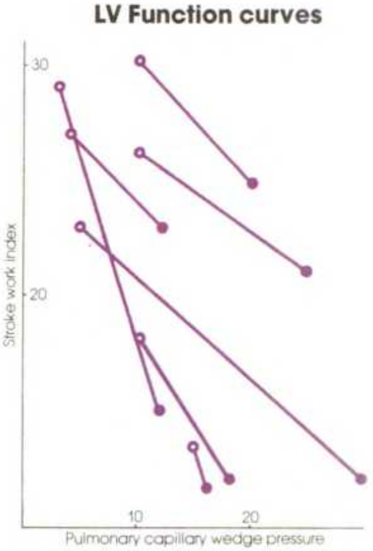


1. Effects of isosorbide dinitrate (Isoket) on pulmonary capillary wedge pressure.

PRIOR TO ISOKET ● ON "OPTIMAL" DOSE OF ISOKET ○



2. Effects of Isoket on cardiac output.



3. Effects of Isoket on left ventricular function curves.

isoket* ampoules

(Isosorbide dinitrate 1mg/ml)

proven effective in heart failure

Isoket was administered i.v. in doses of 2-7 mg/hour to 10 patients suffering from extreme pump failure refractory to conventional therapy. Seven patients had severe coronary disease with recurrent infarctions; 5 receiving Isoket during an acute event and in 3 of them severe mitral regurgitation was documented. Three other patients received Isoket just prior to surgery with heart failure consequent to a ruptured ventricular septum, aortic insufficiency and a severely leaking mitral prosthesis.

Marked haemodynamic improvement during Isoket manifested by decrease of pulmonary wedge pressure (PWP) and systemic vascular resistance with increase of cardiac output was obtained in 7 of the 10 patients studied.

Mean arterial pressure was "markedly and favourably affected in those patients who had high initial pressures. The lower arterial pressures remained stable or even increased a little in two patients." Heart rate and the transmyocardial gradient were not deleteriously affected.

Isoket also produced a complete abolition of the mitral regurgitation as evidenced by the disappearance of the giant 'V' wave on the PWP tracings.

The authors concluded that Isoket appears to be "a highly effective and rather safe drug in properly monitored patients with pump failure."[2]

A copy of this clinical paper, further information and a data sheet are available from:
Sanol Schwarz Pharmaceuticals Ltd.,
The Limes, 130 High Street, Chesham, Bucks. HP5 1EF Tel. (0494) 772071

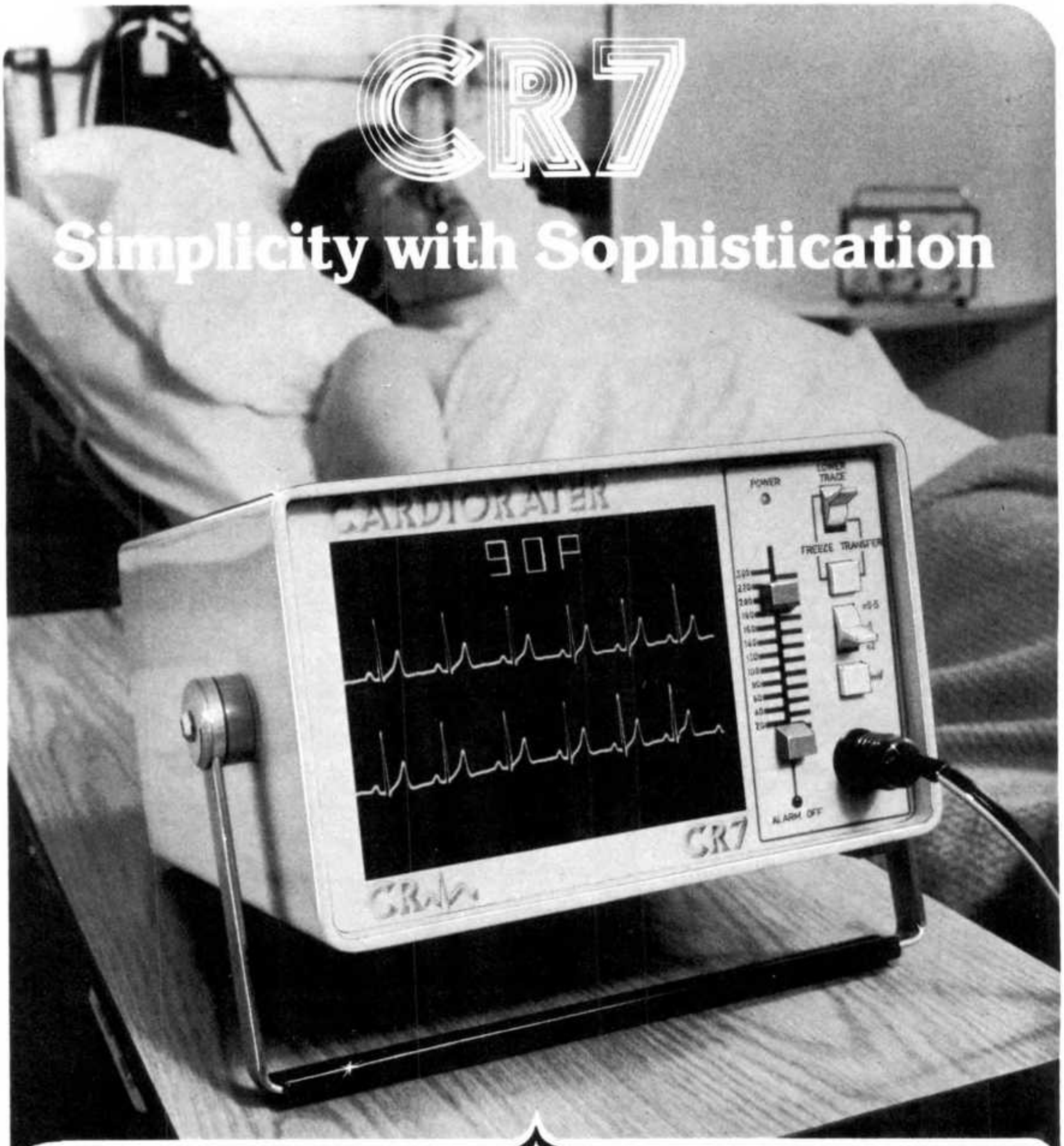
Prescribing Information

Presentation Ampoules containing 10 mg Isosorbide dinitrate in 10 ml of colourless sterile isotonic saline. **Uses** Isoket is indicated in the treatment of unresponsive left ventricular failure secondary to acute myocardial infarction, unresponsive left ventricular failure of various aetiology and severe or unstable angina pectoris. Isosorbide dinitrate is a vasodilator, reducing the afterload and especially the preload of the heart. It influences the oxygen supply to ischaemic myocardium by causing the redistribution of blood flow along collateral channels and from epicardial to endocardial regions. It also reduces oxygen demand by increasing venous capacitance, causing pooling of blood in peripheral veins thereby reducing ventricular volume and heart wall distension. **Dosage and Administration** *Dosage* The dose employed must be adjusted according to the patient's response. In general, a dose of between 2 and 7 mg per hour is suitable, although doses as high as 10 mg per hour may be necessary. *Children* The safety and efficacy of Isoket has not yet been established in children. *Administration* Isoket is a concentrated solution and should never be injected directly. It should always be administered as an intravenous admixture with a suitable vehicle such as Sodium Chloride Injection B.P. or Dextrose Injection B.P. Prepared Isoket admixtures are always given by intravenous infusion or with the aid of an infusion pump. During administration, there should be close monitoring of the patient's blood pressure and pulse. Admixtures are prepared by exchanging the required volume of Isoket with an equal volume of the infusion vehicle. **For example, if a dose of 6 mg per hour is required, 50 ml of Isoket (equivalent to 5 x 10 ml ampoules) should be added to 450 ml of the infusion vehicle to give a final volume of 500 ml. This admixture now contains 1 mg in 10 ml and the required dosage can be obtained by giving 60 ml per hour which is equivalent to a drip rate of 60 paediatric micro-drops per minute or 20 standard drops per minute. This drip rate provides enough solution for an infusion time of 8 hours and 20 minutes. Contra-indications and Warnings, etc.** *Contra-indications* Isoket should not be used in the treatment of cardiogenic shock unless some means of maintaining an adequate diastolic aortic pressure are undertaken. Isoket is contra-indicated in circulatory collapse and severe hypotension. *Precautions* Close attention to pulse and blood pressure is necessary during the administration of Isoket infusions. *Adverse Effects* Whilst sharp falls in systemic arterial pressure can give rise to symptoms of cerebral flow deficiency and decreased coronary perfusion, clinical experience with Isoket has shown that this is not normally a problem. This is consistent with the known vasodilatory effects of Isosorbide dinitrate which occur predominantly on the venous rather than the arterial side of the circulation. In common with other nitrates, headache and nausea may occur during administration. **Pharmaceutical Precautions** *Compatibility* **Isoket contains Isosorbide dinitrate in isotonic saline and is compatible with commonly employed infusion solutions. No incompatibilities have so far been demonstrated. Isoket is compatible with glass infusion bottles and infusion packs made of polyethylene, e.g. Polyfusor (Boots) or Bottle-Paks and Flat-Paks distributed by Dylade, Cheshire. Isoket may be infused slowly using a syringe pump with a glass or rigid plastic syringe (Gillette Sabre syringe or Brunswick Disposable Plastipak syringes).** Isoket is incompatible with infusion bags and administration sets made from PVC and a loss of activity of up to 40% is possible on prolonged contact, e.g. 8 hours. Loss after 1 hour is approximately 30%. The use of PVC containers should therefore be avoided, e.g. Viaflex (Travenol) or Steriflex (Boots). **Legal Category** POM. **Package Quantities** Each pack contains ten ampoules of Isoket. **Further Information** Nil. **Product Licence** PL 4438/0001. **Basic NHS Cost** £49.50 per pack of 10 ampoules.

SANOL
SCHWARZ

*Trade Mark

1. W.W. Parmley and K. Chatterjee: "In coronary care: Congestive heart failure." American Heart Association (1977).
2. Rabinowitz B et al, In Nitrates II, 2nd Int. Nitrate Symp., Eds. Rudolph & Schrey, Urban & Schwarzenberg (1980).



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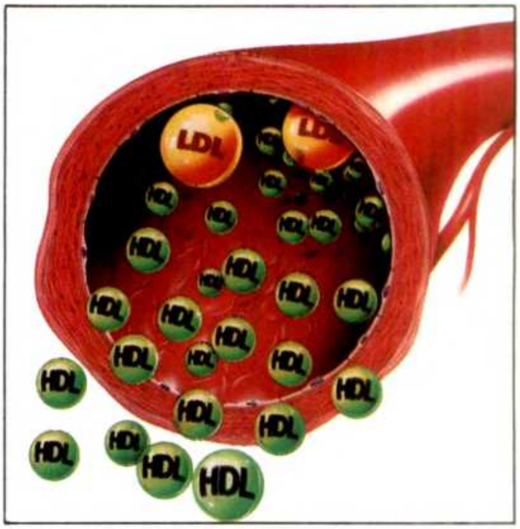
Low levels of HDL are associated with an increased risk of CHD.[1] Patients who fail to respond adequately to diet may benefit from Bezalip which raises HDL whilst lowering excessive cholesterol, triglyceride, LDL and VLDL. Many treatments, including diet, have no known effect on or even adversely affect HDL.[2]

Bezalip also reduces elevated platelet aggregation[3] and blood viscosity.[4] There is no evidence that Bezalip will increase the risk of developing gallstones.[5] Bezalip is very well tolerated. In a one year study of 1091 patients, only 3.4% terminated treatment because of side effects.[6]



New

Bezalip

bezafibrate

Bezalip has been shown to be more effective than clofibrate in reducing cholesterol, triglyceride, LDL and VLDL and in raising the protective factor HDL[1,2]

Prescribing Information: Presentation Bezalip tablets each containing 200mg bezafibrate. **Indications** Therapy in fully diagnosed hyperlipidaemic states (Fredrickson types IIa, IIb, III, IV & V) which warrant treatment and do not respond adequately to diet alone. **Dosage** 3 tablets (600mg bezafibrate) daily in divided doses. **Contra-indications** Severe hepatic and renal dysfunction, nephrotic syndrome, primary biliary cirrhosis. Not recommended in pregnant or breast feeding women. **Warnings & Precautions** Dosage of anti-coagulant therapy should be reduced to 50% initially and then titrated to the patient's response. A reduced dosage of Bezalip is required in mild to moderate renal dysfunction. Adverse effects rarely occur; may include feelings of fullness of the stomach, a myositis-like syndrome, disorders of potency and hypersensitivity. No increase in cholelithiasis. **Packs and Basic NHS Cost** Packs of 100 & 500 tablets. 100 tablets, £10.56. **Product Licence Number** PL0075/0036. Further information available on request.

1. *JAMA*, **62** (1977) 707
2. Manufacturers' Literature
3. Lipoproteins and Coronary Heart Disease, Witzstrock Publishing House, New York (1980) 185-188
4. *Ibid.* 192-195
5. *Munch. med. Wschr.* **122, 5** (1980) 165-168
6. Diet and Drugs in Atherosclerosis, eds. G. Noseda, B. Lewis, R. Paoletti, Raven Press, New York (1980) 137-142

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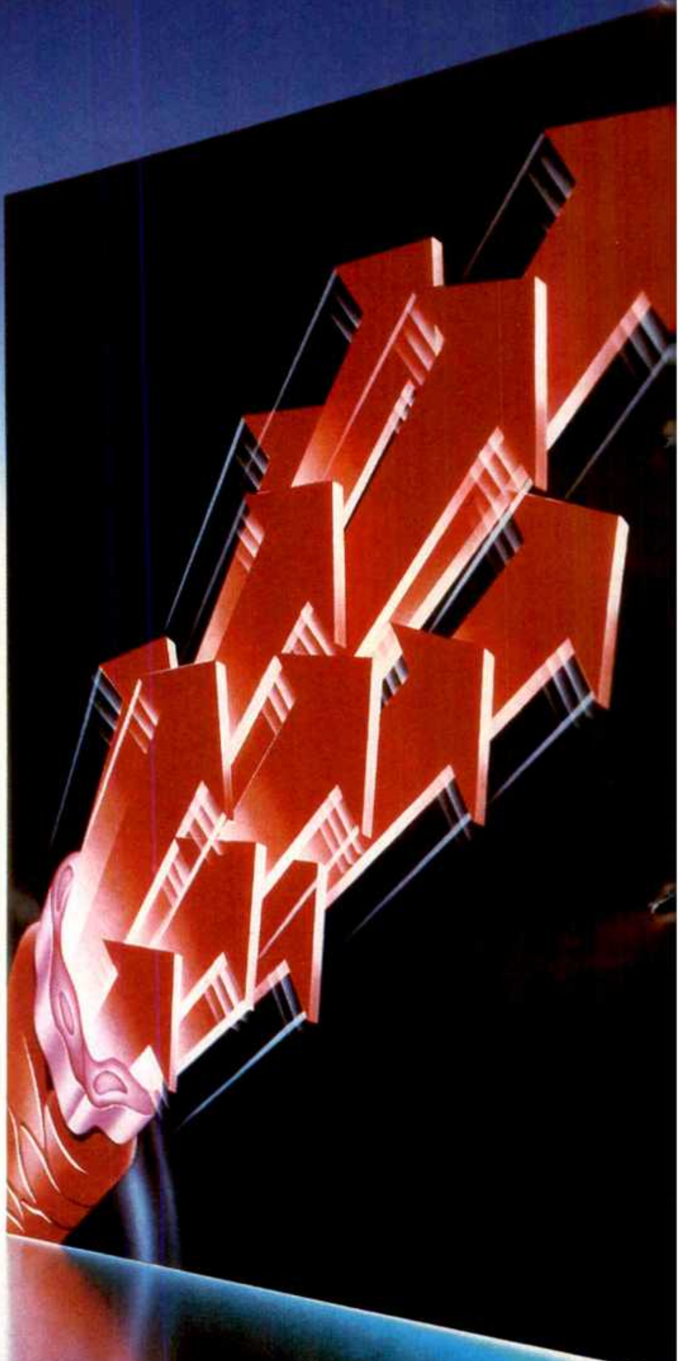


Hypertension

In patients with moderate to severe hypertension, one of the fundamental treatment problems is that titrating up with beta-blockers or diuretics can result in an increase in side-effects.

However, when Hypovase is added to first-line therapy, mean arterial pressure, total peripheral resistance and haemodynamic profile are all improved – without a corresponding increase in side-effects.

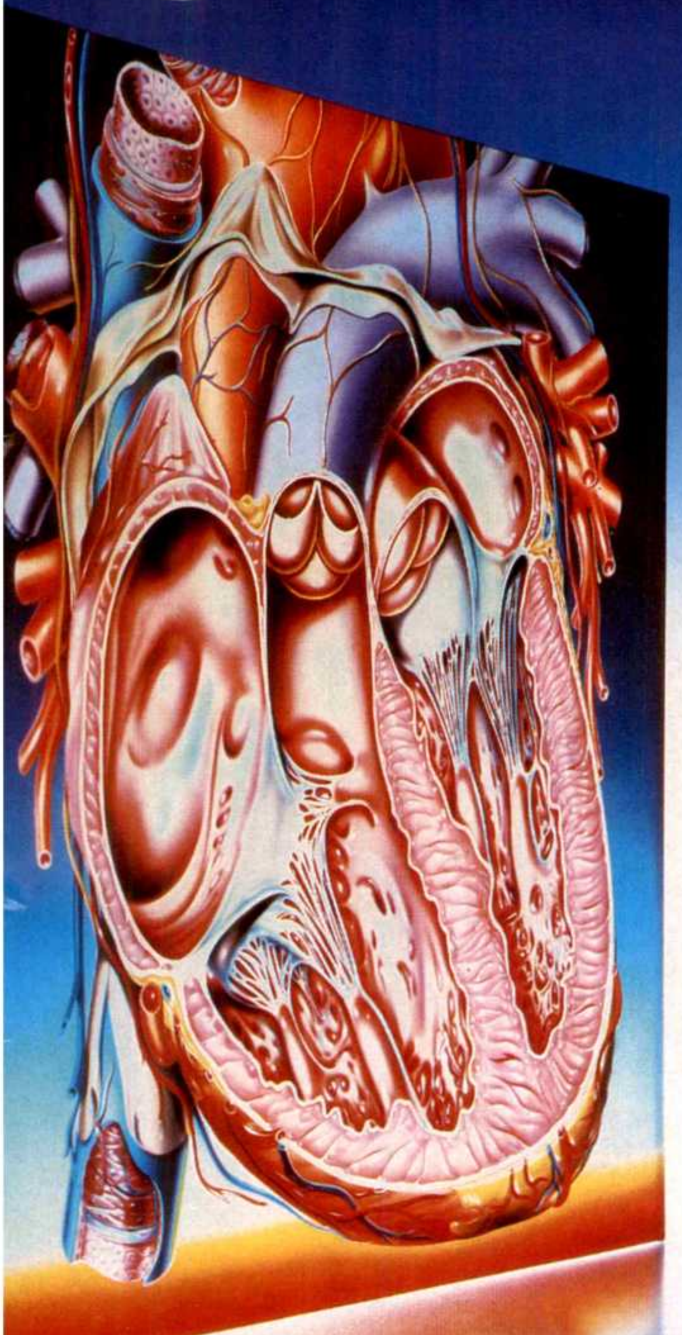
A study of patients with poorly controlled hypertension showed that reductions of 57/27 mm Hg and 29/21 mm Hg[1] were achieved when Hypovase was added to beta-blocker or diuretic therapy respectively.

A further long-term study[2] confirmed these findings, and also demonstrated that no tolerance developed to these regimens at 15 month's follow-up.

Hypovase*
prazosin HCl

boosts beta-blocker
or diuretic therapy.

major indications.



Congestive heart failure.

One of the major therapeutic goals in treating congestive heart failure is to reduce both preload and afterload.

Hypovase has been shown to achieve this goal.

"Oral prazosin resulted in a rapid and sustained reduction in pulmonary congestion with striking improvement in the symptoms of cardiac failure. Further, there were no side-effects during our trial."[3]

"Prazosin would appear to have reduced aortic impedance and left ventricular filling pressure resulting in increased cardiac output and stroke volume."[4]

In addition, clinical studies have shown that Hypovase increases cardiac index – raising exercise tolerance and reducing fatigue.

Hypovase – reduces preload and afterload and improves cardiac performance.[3,4]

Hypovase*

prazosin HCl

boosts patient activity.

1. Turner, A.S., et al. Med. J. Aust., Spec., Suppl., (1977), **2**, 33-37.
2. Fauchald, P., et al. Excerpta Medica International Symposium, Vienna, November (1978), 85-93.
3. Bossi, M, et al. Excerpta Medica Symposium, Tokyo (1978), 107.
4. Hutton, I, et al. European Prazosin Symposium (1978), 138.

Prescribing Information

Indications Hypertension of varied aetiology and all grades of severity, congestive heart failure of moderate to severe degrees.

Contra-Indications Sensitivity to Hypovase.

Precautions A low initial dose and gradual titration is recommended. A small percentage of patients may react more rapidly and to a greater extent than the majority. In some cases this has led to sudden loss of consciousness generally lasting a few minutes. Subsequent treatment may be satisfactory. Hypovase is not recommended in pregnancy, during lactation or in children under 12 years of age.

Side Effects Dizziness, drowsiness and lack of energy are the most common.

Dosage

Congestive Heart Failure Suggested Initial Daily Dose Range: 0.5mg increasing to 1.0mg t.i.d., or q.i.d. Usual Daily Maintenance Dose: 4.0mg to 20mg in divided doses.

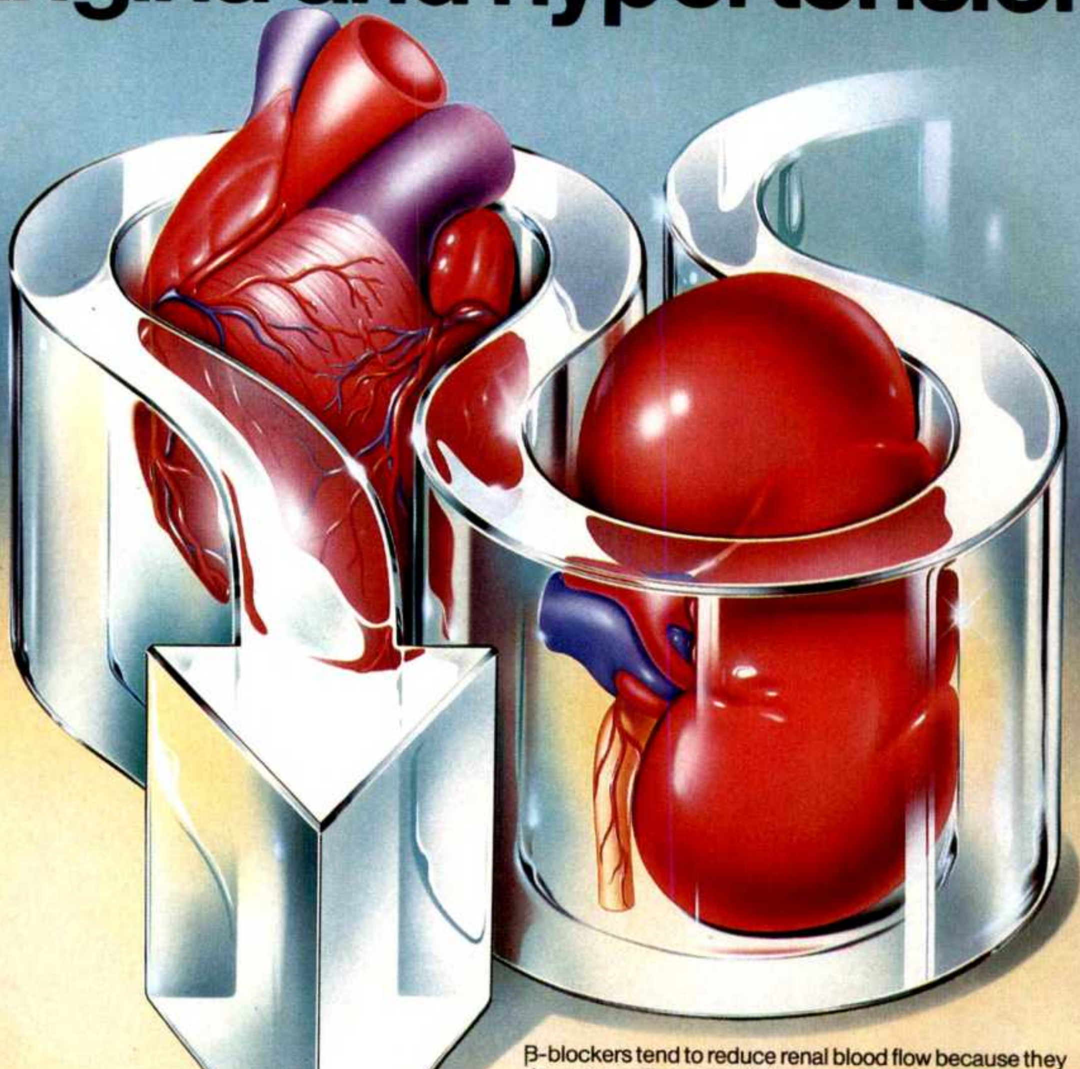
Hypertension Starting dose 0.5mg two to three hours before retiring; thereafter up to 20mg/day in divided doses. Twice daily dosing is usually adequate.

Basic N.H.S. Cost 0.5mg tablet (PL57/0149) pack of 100, £4.08; 1mg tablet (PL57/0106) pack of 100, £5.25; 2mg tablet (PL57/0107) pack of 100, £8.98; 5mg tablet (PL57/0108) pack of 100, £15.58.

Also available is a b.d. Starter Pack, for hypertension only, containing 8x0.5mg and 32x1mg Hypovase tablets, £2.70.

Full information on request

All round protection in angina and hypertension



β-blockers tend to reduce renal blood flow because they depress cardiac output.[1] Corgard differs from other β-blockers in not reducing renal function.[2,3] The mechanism is uncertain but one possibility is that this agent is a direct renal vasodilator.[2] Choose Corgard and be assured of protecting renal function as well as protecting the heart.

Corgard™
nadolol

Protects the heart-protects renal function

Further information is available from: Technical Services Department, E.R. Squibb & Sons Ltd., 141–149 Staines Road, Hounslow, Middlesex TW3 3JA.

SQUIBB™

See overleaf for full prescribing information.

Corgard

nadolol

tablets

Prescribing Information

Presentation White round biconvex tablets. 80 mg: scored on one side and engraved "Squibb" '241' containing nadolol 80 mg, 40 mg: engraved "Squibb" '207' containing nadolol 40 mg. **Indications** Corgard is indicated in the long-term management of angina pectoris and hypertension. **Dosage and administration** Dosage should be individually titrated. In elderly patients, particularly those with angina pectoris, a low initial dose should be used so that sensitivity to side effects may be assessed. Nadolol may be given in a once daily dosage without regard to meals. Angina Pectoris: Initially 40 mg once daily. This may be increased at weekly intervals until an adequate response is obtained or excessive bradycardia occurs. Most patients respond to 160 mg or less daily. The value and safety of daily doses exceeding 240 mg have not been established. Hypertension: Initially 80 mg once daily. This may be increased by a weekly increment of 80 mg or less until an optimum response is obtained. Most patients respond to 240 mg or less, daily, but doses up to 640 mg have been required for a few patients. In some patients it is necessary to administer a diuretic, peripheral vasodilator and/or other anti-hypertensive agent in conjunction with nadolol in order to achieve satisfactory response. Treatment of hypertension associated with phaeochromocytoma may require the addition of an alpha-blocking agent. **Contra-indications** Bronchial asthma, sinus bradycardia and 2nd and 3rd degree heart block; cardiogenic shock; right ventricular failure secondary to pulmonary hypertension; congestive heart failure. **Warnings** The normal precautions associated with the use of beta-adrenergic blockers should be followed. Exacerbation of angina and myocardial infarction have occurred after abrupt discontinuation of therapy with beta-adrenergic blocking agents in patients with angina pectoris or other evidence of coronary artery insufficiency. When discontinuing long-term nadolol therapy the dosage should be reduced gradually over a period of at least two weeks. There have been reports of skin rashes and/or dry eyes associated with the use of beta-adrenergic blocking drugs. The reported incidence is small and in most cases the symptoms have cleared when the treatment was withdrawn. Discontinuance of the drug should be considered if any such reaction is not otherwise explicable. Caution is advised in the presence of impaired renal or hepatic function, obstructive airways disease and diabetes mellitus. Care should be taken in administering nadolol during and within 2 weeks of administration of adrenergic augmenting psychotropic drugs such as monoamine oxidase inhibitors. The safety of nadolol in pregnancy has not yet been established, and nursing mothers should only receive nadolol if deemed essential. **Side-effects** These resemble those reported with other beta-blocking drugs and rarely require withdrawal of treatment. Those reported infrequently include gastro-intestinal effects, bradycardia, fatigue, light-headedness, cold extremities, insomnia, paraesthesia and dryness of the mouth. Cardiac insuffiency, hypotension and AV block have occurred on rare occasions. **Overdosage** Overdosage or exaggerated response should be treated supportively and symptomatically. **Legal category** Prescription only. **Product Licence Numbers** 80 mg – 0034/0186 40 mg – 0034/0185. **Package Quantities** Bottles of 100 tablets. Cost per 80 mg tablet, 16p. Cost per 40 mg tablet, 11p. ▼ Special reporting to CSM required. Corgard is a Trade Mark of E.R. Squibb & Sons Ltd.

References

1. Lancet 1980; 1: 693 2. Br J clin Pharm 1979; 7: (Suppl 2) 219S 3. In: Gross F, ed. International Experience with Nadolol – a long-acting ß-blocking agent: symposium, Paris, December 5–7, 1980 London: R Soc Med No 37 1981 25–30

Further information available from: Technical Services Department, E.R. Squibb & Sons Ltd., Squibb House, 141–149 Staines Road, Hounslow, TW3 3JA.

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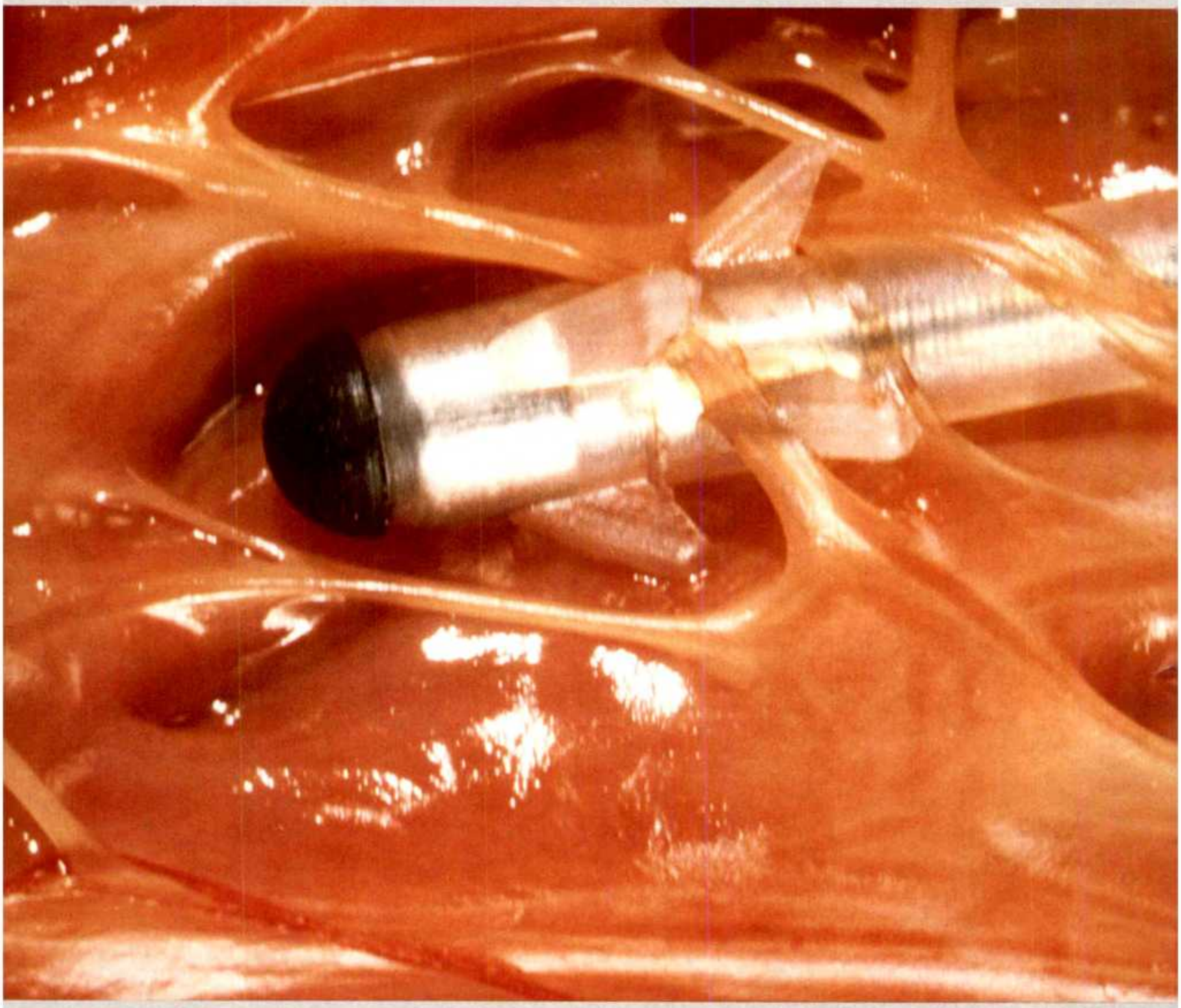
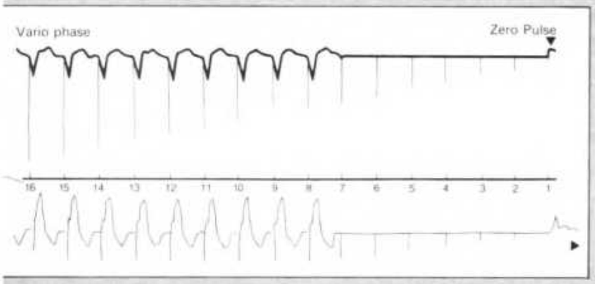


Siemens - Pacemakers are our business

Implantable pacers - in action since 1958

Siemens-Elema were the pioneers of cardiac pacemakers; indeed, in 1958 we were the only company in he world offering an implantable pacemaker for general clinical use. Today we are still in the forefront of pacemaker development. For example, the multi-programmable model 668 used in combination with he vitreous carbon-tip lead, has many significant advantages, all adding up to a truly universal pacemaker system for multi-purpose clinical use.



The systems approach

The design philosophy behind the model 668 is the systems approach; a technique which has been applied on all the component parts and ancillary systems. This makes the system superior, not just in terms of unction, but also in terms of quality, esting, reliability and cost.

Versatility & reliability

Two incompatible qualities for a pacemaker? – Perhaps at first sight, but when one realises the amount of development that has gone into the 668 pacemaker system then the claim is fully justified.

The 668 pulse generator can be programmed to meet most pacing requirements and is, therefore, probably the most versatile unit currently available.

The adjustable pulse duration and variable pulse amplitude in combination with the low-threshold carbon-tip lead affords the model 668 prolonged service life, with maintained safety margins.

Programmability – and the ease of re-programming if the patient's heart condition changes – ensures safe, efficient pacing and the optimum utilisation of battery capacity.

Programmability and Vario ® function

The 668 generator can be programmed for the six key parameters: pulse rate, pulse duration, pulse amplitude, sensitivity, refractory period and hysteresis. In addition, the 668 has the unique Vario function – a non-invasive technique for determining the true voltage threshold. The Vario cycle, which is initiated by the test magnet, consists of 15 pulses of decreasing amplitude. Knowing the difference in each step, it simply becomes a matter of counting the pulses on the EKG – strip which does not depolarise the heart. The figure multiplied by the known voltage difference between the steps, gives you the true voltage threshold.

The 668 has several features not found in other multi-programmable pacers:– The unique Vario system, 10V output for high threshold patients, distinct ERT criteria and the possibility of dual demand function.

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Many of the clinical complications encountered in pacemaker therapy are in one way or another related to the pacing lead. Siemens-Elema has come up with what may prove to be the solution to such complications as exit blocks and sensing difficulties. Our answer to these problems is the vitreous carbon-tip.

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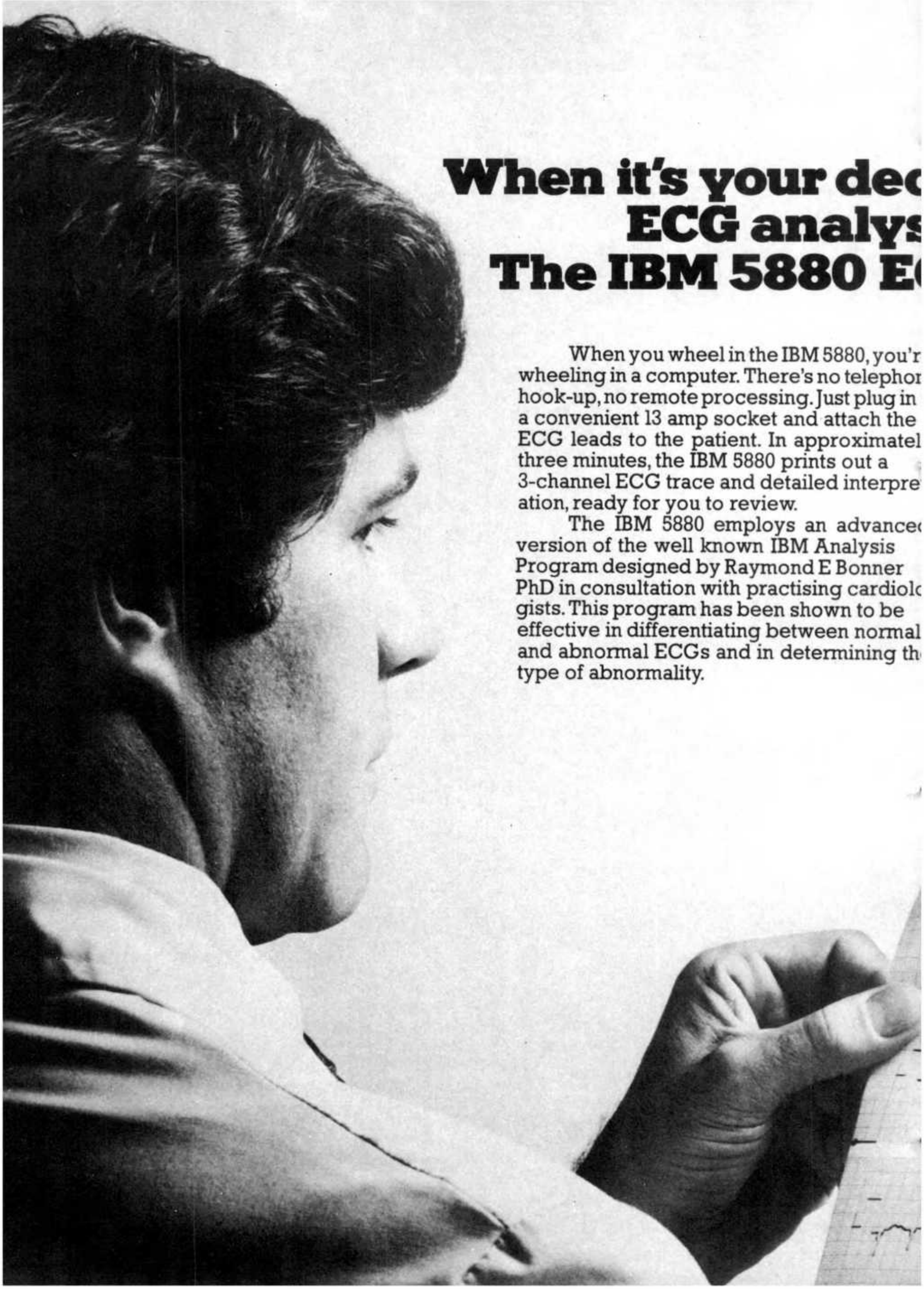

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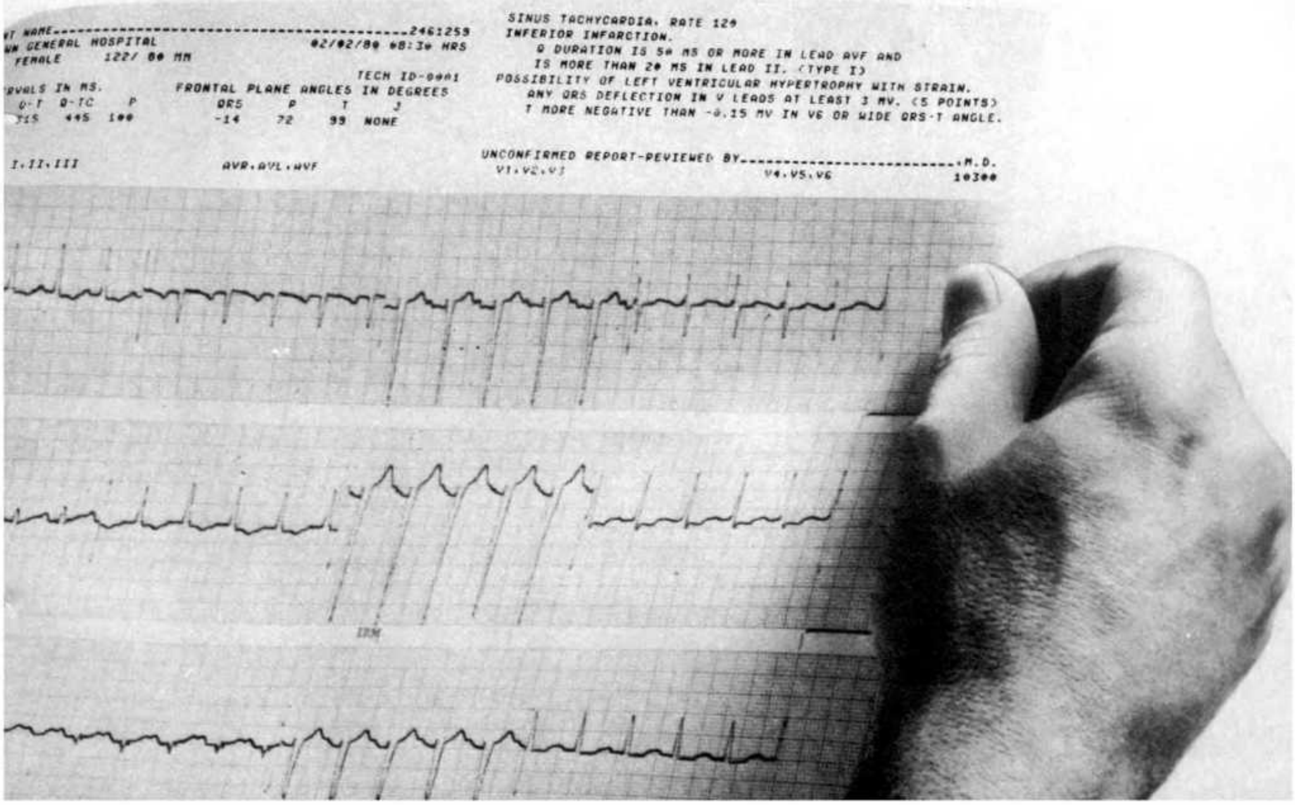

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                                                   TECH ID-00A1  POSSIBILITY OF LEFT VENTRICULAR HYPERTROPHY WITH STRAIN.
RVALS IN MS.          FRONTAL PLANE ANGLES IN DEGREES             ANY QRS DEFLECTION IN V LEADS AT LEAST 3 MV. (5 POINTS)
 Q-T  Q-TC    P              QRS     P     T      J               T MORE NEGATIVE THAN -0.15 MV IN V6 OR WIDE QRS-T ANGLE.
 315   445  100              -14    72    99   NONE

                                                              UNCONFIRMED REPORT-REVIEWED BY----------------------------,M.D.
 I,II,III                    AVR,AVL,AVF                        V1,V2,V3                        V4,V5,V6              10300
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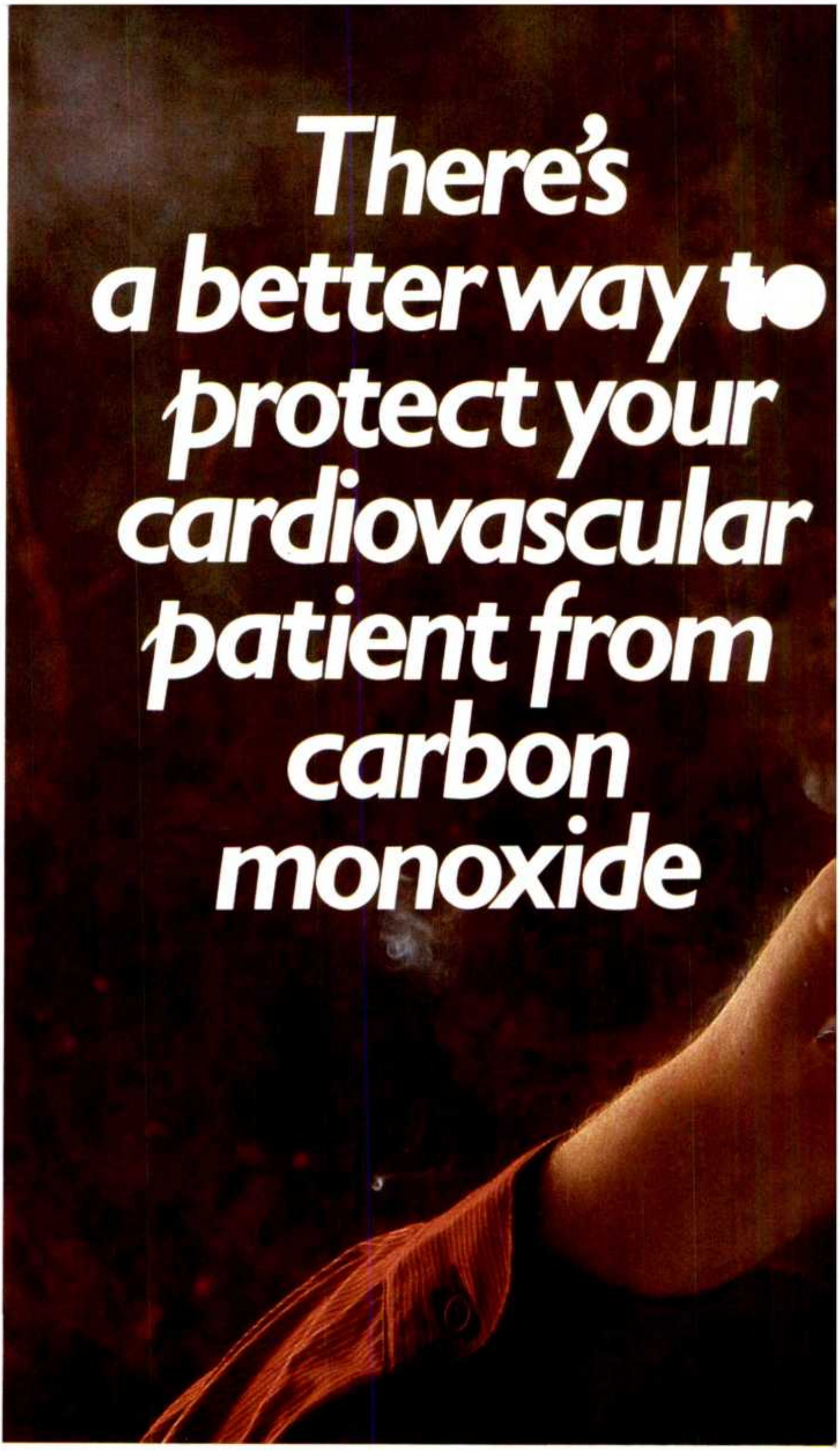

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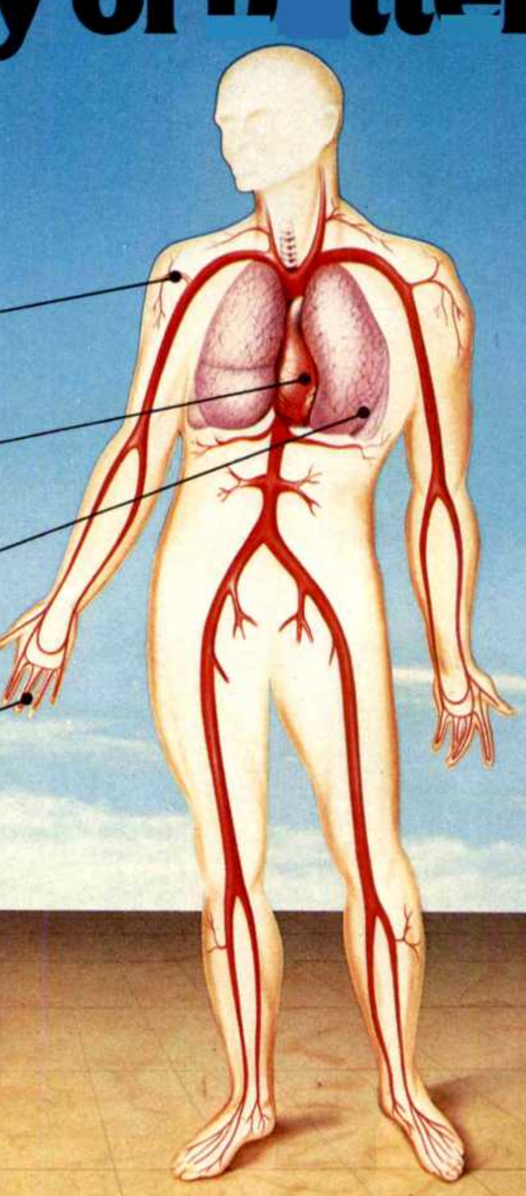

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0) *Pharmacology of anti-hypertensive drugs*. Ed. Scriabine, A. Raven Press, N.Y. 161. 2. Coltart, J. (1981) *Brit. J. Clin. Pharmacol.*, **12**. 3. Zacharias, F.J. (1981) *Brit. J. Clin. Pharmacol.*, **12**. 4. Fitzgerald, M.V.J.
1) *Brit. J. Clin. Pharmacol.*, **12**. 5. Johnson, E.S. (1981) *Brit. J. Clin. Pharmacol.*, **12**. Further information is available on request. **Wyeth Laboratories**, John Wyeth & Brother Ltd., Taplow, Maidenhead, Berks.
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Br Heart J 1982; 47: 109–121

Assessment of atrioventricular septal defects by two dimensional echocardiography

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SUMMARY Ninety-six patients with an atrioventricular septal defect were assessed by two dimensional echocardiography. Forty-eight patients were judged as having two discrete valve orifices. In this group, 37 had an intact ventricular septum and 11 a ventricular septal defect. Two patterns of attachment of the valve leaflets to the interventricular septum were noted. Forty-eight patients had a common valve orifice. In 29 patients there was absence of tethering of the anterior bridging leaflet to the interventricular septum. A further 19 had varying degrees of tethering of the anterior bridging leaflet. A ventricular septal defect was identified under the anterior bridging leaflet in all cases. In 58 cases where the posterior bridging leaflet was identified, a ventricular septal defect was visualised in eight and missed in two.

Seventy-eight patients had an ostium primum defect, 12 a common atrium, and a further six an intact interatrial septum. Two dimensional echocardiography provides in depth morphological information about the type of atrioventricular defect and can correctly identify the presence of a ventricular septal defect beneath the anterior or posterior bridging leaflet, unless it exists between short crowded chordae.

The assessment of the atrioventricular junction is readily achieved by two dimensional echocardiography. Since atrioventricular septal defects are primarily an abnormality of this region, reliable delineation of their detailed morphology should be possible by this technique. Indeed, Hagler *et al.*[1] showed that, using echocardiography, it was possible to identify with reasonable accuracy "partial" atrioventricular septal defects, together with the three varieties of "complete" defect described by Rastelli *et al.*[2]

The Rastelli classification has the great merit of simplicity, and has for many years been used for reporting surgical results. More recently its value in this respect has been questioned.[3] Furthermore, it describes only one aspect of atrioventricular septal defects, being based on the morphology of the anterior bridging leaflet, and does not allow for description of the so-called "transitional forms" which undoubtedly exist in addition to the "partial" and "complete" varieties.[4] Full description of an atrioventricular septal defect depends on identifying all abnormalities of the valve orifice, valve leaflet tissue, and tension apparatus, in addition to describing the interatrial and interventricular communications if present.[5 6] Associated abnormalities are then tabulated. This study was carried out in order to see whether two dimensional echocardiography could reliably describe all these anatomically observed features of atrioventricular defects, thus permitting descriptive rather than procrustean categorisation.

Subjects and methods

Ninety-six cases of atrioventricular septal defect were examined routinely during a 12 month period at The Hospital for Sick Children, Great Ormond Street. Patients with univentricular hearts and common atrioventricular orifice were excluded, these having been described elsewhere.[7] In the majority the diagnosis was unknown at the time of examination, but in some, cardiac catheterisation and angiocardiography had previously been performed.

The children were examined using an Advanced Technology Laboratory Mechanical Sector Scanner, with a 3·0 or 5 MHz transducer. Both the apical and subcostal four chamber views were used. The former

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approach visualised most clearly the more anterior (Fig. 1), and the latter the more posterior part of the interventricular septum (Fig. 2).

The presence of an interventricular communication beneath the posterior bridging leaflet was determined, firstly from a subcostal four chamber cut and then by clockwise rotation of the transducer into the long axis. In the former cut the posterior bridging leaflet could be seen (Fig. 2). With clockwise rotation of the transducer the anterior leaflet and its attachment to the left ventricular outflow tract was visualised. In addition, the posterior bridging leaflet could be seen in this cut (Fig. 3) and during real-time assessment its chordal attachments to the septum were noted.

Presence or absence of an interventricular communication beneath the anterior bridging leaflet could best be assessed in the apical four chamber view. The insertions of the anterior bridging leaflet within the right and left ventricles were also determined in this cut. The extent and integrity of the interatrial septum and the presence of associated defects were assessed by combining standard views as previously described.[8]

The anatomy observed is described using the nomenclature proposed by Piccoli *et al.*[5 6] The criteria used for angiocardiographic analysis, and specifically those differentiating defects beneath the anterior and posterior bridging leaflets, were those indicated by Macartney *et al.*[9]

Results

ATRIOVENTRICULAR SEPTAL DEFECTS WITH SEPARATE VALVE ORIFICES

Forty-eight patients had two discrete atrioventricular orifices as assessed by two dimensional echocardiography. In 37 of these the bridging leaflets and the connecting tongue between them were firmly attached to the crest of the ventricular septum so that no interventricular communication was present. Two patterns of attachment of the bridging leaflets and connecting tongue to the septum were identified.

In 20 the anterior bridging leaflet was itself turned in and firmly adherent to the crest of the septum along its length (Fig. 4). In 17 further cases the anterior interventricular component was blocked by longer, but tightly packed or fused chordae between the bridging leaflet and the crest. In six of these the chor-

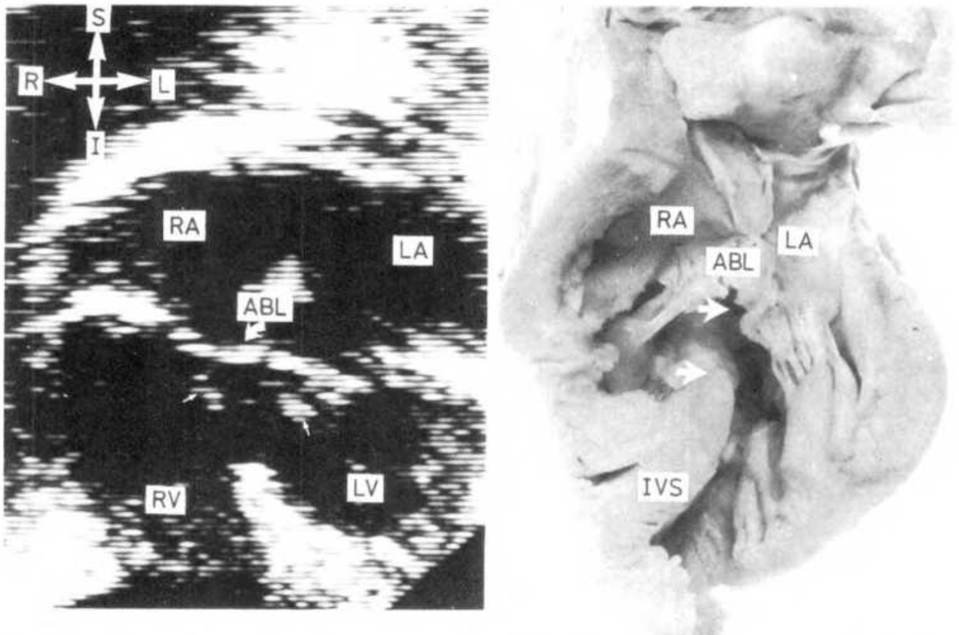

Fig. 1 *The left hand panel is an apical four chamber cut in a case with a common atrioventricular orifice and a free floating anterior bridging leaflet. Note the absence of chordal attachments to the interventricular septum. The small arrows point to the chordal attachments of the leaflet. The right hand panel is a specimen with a common atrioventricular orifice, illustrating the echocardiographic features on the left. The white arrows indicate the ventricular septal defect. ABL, anterior bridging leaflet; IVS, interventricular septum; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.*

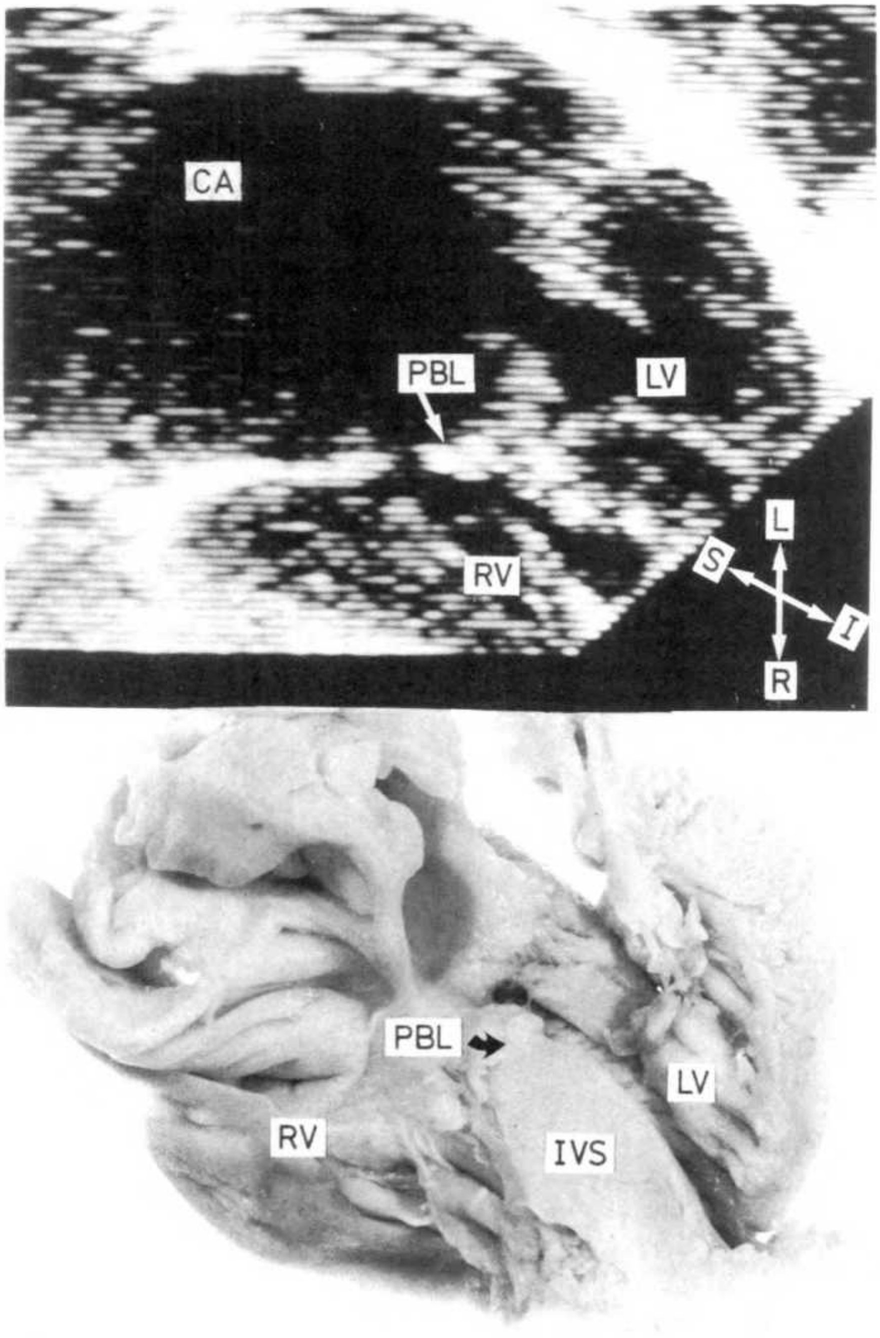

Fig. 2 *The upper panel is a subcostal four chamber cut, with the transducer angled posteriorly. The attachment of the posterior bridging leaflet at the crux of the heart can be seen. The lower panel is a different anatomical specimen showing the posterior bridging leaflet attached at the crux of the heart. Note, here the septum secundum is present. CA, common atrium; PBL, posterior bridging leaflet. See Fig. 1 for remaining abbreviations.*

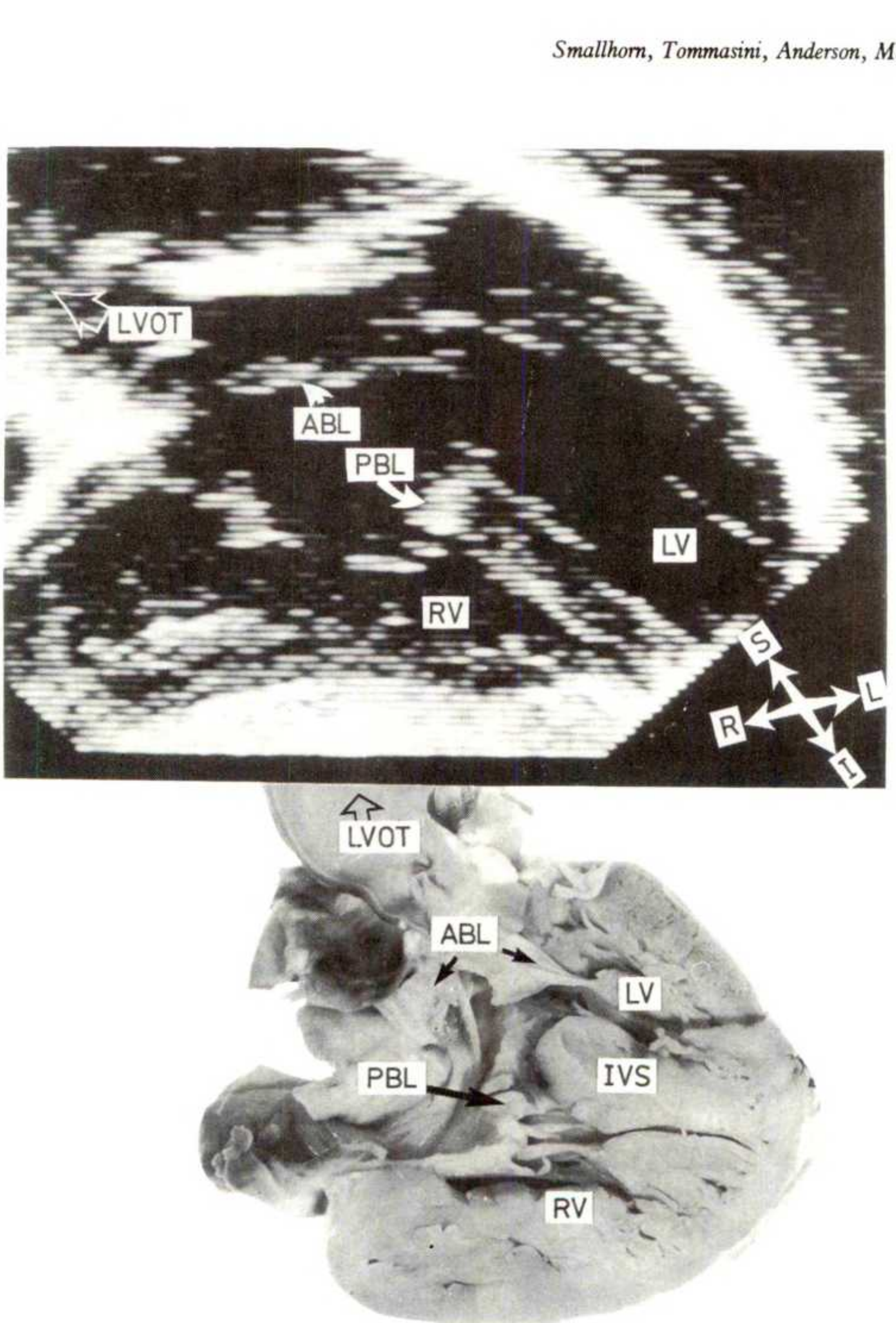

Fig. 3 *The upper panel is a subcostal long axis cut showing the anterior and posterior bridging leaflets. Note the posterior bridging leaflet is attached to the posterior part of the interventricular septum and the anterior bridging leaflet to the left ventricular outflow tract. The lower panel is a specimen cut in a long axis view to show the attachments of the anterior and posterior bridging leaflets. LVOT, left ventricular outflow tract. See Fig. 1 for remaining abbreviations.*

dae inserted onto the septal crest, while in 11 they inserted immediately to the right of the septal crest (Fig. 5). Even during real-time examination, no defects could be seen under the anterior bridging leaflet of these patients. In this group, confirmation of the lesion was possible in 35 patients at either cardiac catheterisation, surgery, and/or necropsy.

In 11 cases, a communication was found between the valve leaflets and the septal crest. All had associated "clefts" in the left sided atrioventricular valve and in two cases surgical confirmation of an atrioventricular defect was possible. In five the atrioventricular valves appeared to be attached to a structure in between the interatrial and interventricular communications (Fig. 6).

Table 1

	AV defects with separate orifices (No. 48)	*AV defects with a common orifice (No. 48)*
Ostium primum	39 (81%)	39 (81%)
Intact atrial septum	6 (13%)	
Common atrium	3 (6%)	9 (19%)

Of the cases with two separate atrioventricular orifices, six had an intact atrial septum as judged echocardiographically (Table 1), the lower edge of the septum extending down to the closure plane of the atrioventricular valve leaflets. At operation one of these patients had a very small anterior interatrial defect plugged by the anterior bridging leaflet. In two further cases the lower edge of the atrial septum extended almost to the level of the atrioventricular valves but was slightly displaced to the left. During invasive investigation the catheter appeared to pass directly from the right atrium to the left ventricle, and in one of these the left atrium could not be entered. Thirty-seven cases had a more generous and typical ostium primum atrial septal defect, while in the final three there was a common atrium (Figs. 4 and 6).

ATRIOVENTRICULAR SEPTAL DEFECTS WITH COMMON ATRIOVENTRICULAR ORIFICE

Forty-eight patients were judged to have non-partitioned orifices by two dimensional echocardiography. In 29 cases there was absence of tethering of

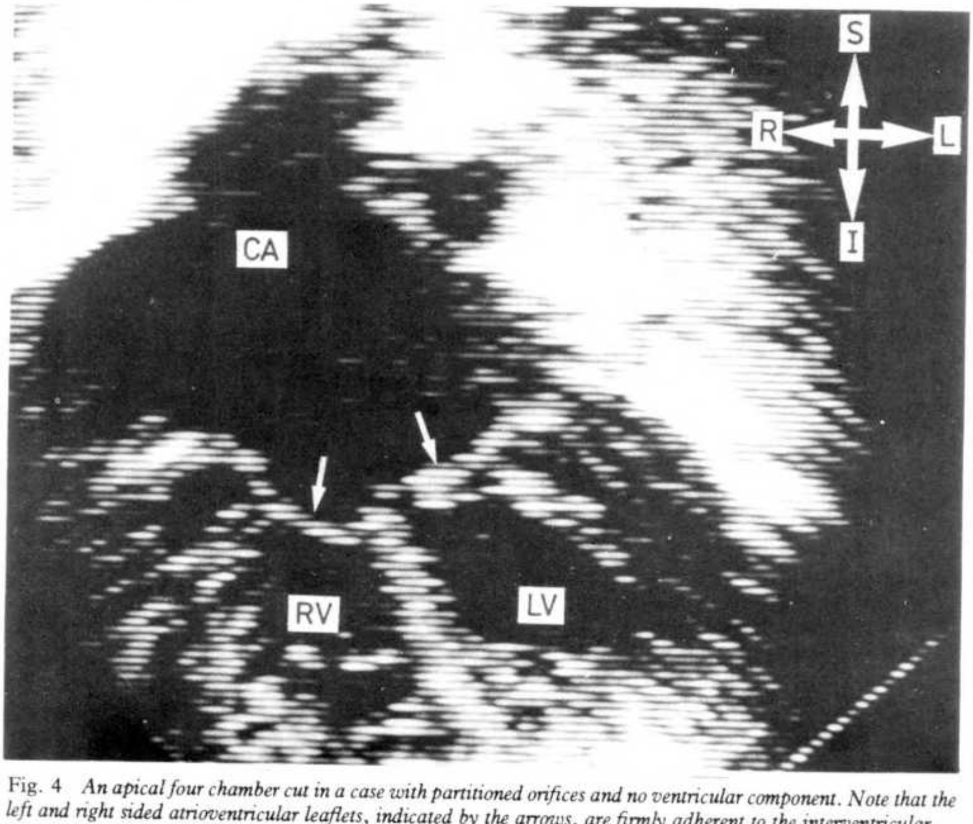

Fig. 4 *An apical four chamber cut in a case with partitioned orifices and no ventricular component. Note that the left and right sided atrioventricular leaflets, indicated by the arrows, are firmly adherent to the interventricular septum. See Figs. 1 and 3 for abbreviations.*

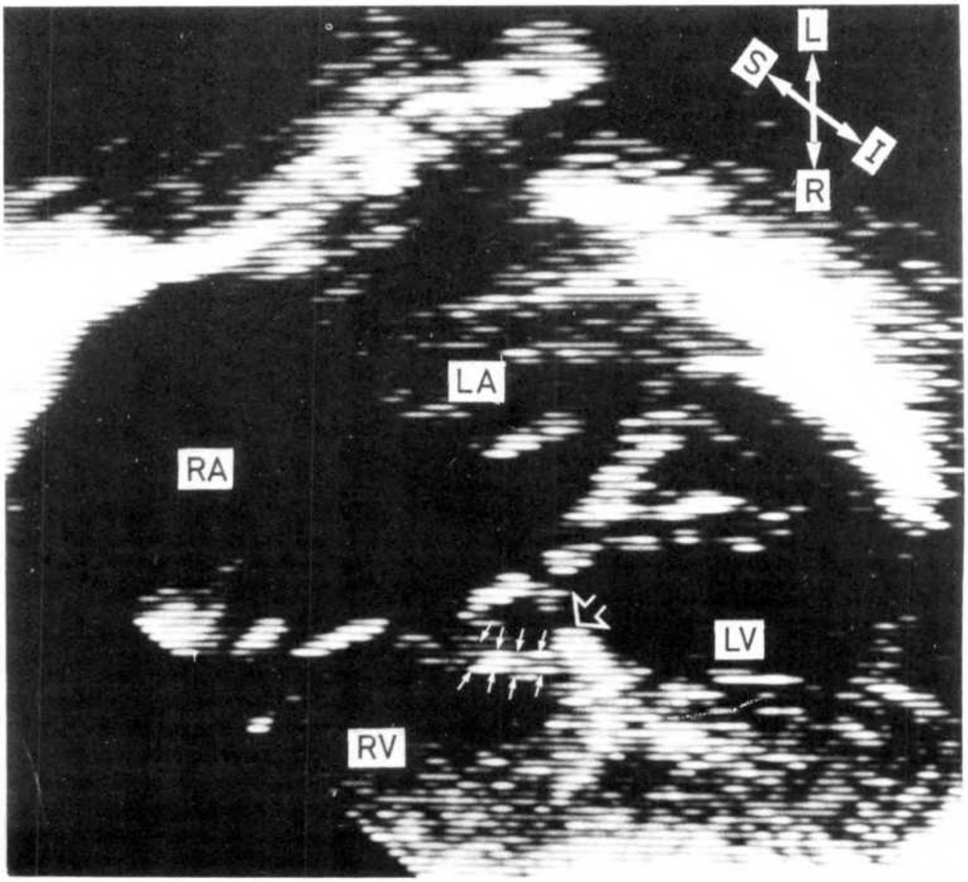

Fig. 5 *An apical four chamber cut in a case with partitioned orifices and no ventricular component. Note that the chordae, indicated by small arrows, are inserted into the right side of the interventricular septum. The large open arrow points to the crest of the interventricular septum. See Fig. 1 for abbreviations.*

the anterior bridging leaflet to the interventricular septum (Fig. 1). Nine patients had long thin chordae, tethering the anterior bridging leaflet to the crest of the interventricular septum so as to divide it into equal parts (Fig. 7). In five the chordae from the anterior leaflet were tethered to the right side of the crest of the septum (Fig. 8), with the papillary muscle insertion being at its base. Five others had the same papillary muscle insertion, but no chordae tethering the anterior leaflet were seen.

An interventricular communication was seen in all patients beneath the anterior bridging leaflet in the apical four chamber view. Surgical, necropsy, or angiocardiographic confirmation of this finding was available in 37 patients.

In 41 patients in whom the posterior septum was clearly visualised and independent confirmation of the diagnosis was available, an interventricular defect beneath the posterior bridging leaflet was correctly diagnosed in four patients and missed in two (Fig. 9). Absence of such a defect was correctly diagnosed in the other 35 patients. In a further group of 17 patients without other confirmatory evidence, a posterior defect was visualised in three and was absent in the remainder.

INTEGRITY OF ATRIAL SEPTUM

Nine patients with a common atrioventricular orifice had a common atrium and 39 had an ostium primum defect of varying size (Table 1). In no case did the interatrial septum extend to the level of the atrioventricular annulus.

PAPILLARY MUSCLES AND MITRAL "CLEFTS"

In all cases, regardless of whether the atrioventricular orifice was partitioned or not, two papillary muscles in the left ventricle were identified in the short axis view. A "cleft" in the left sided atrioventricular valve was

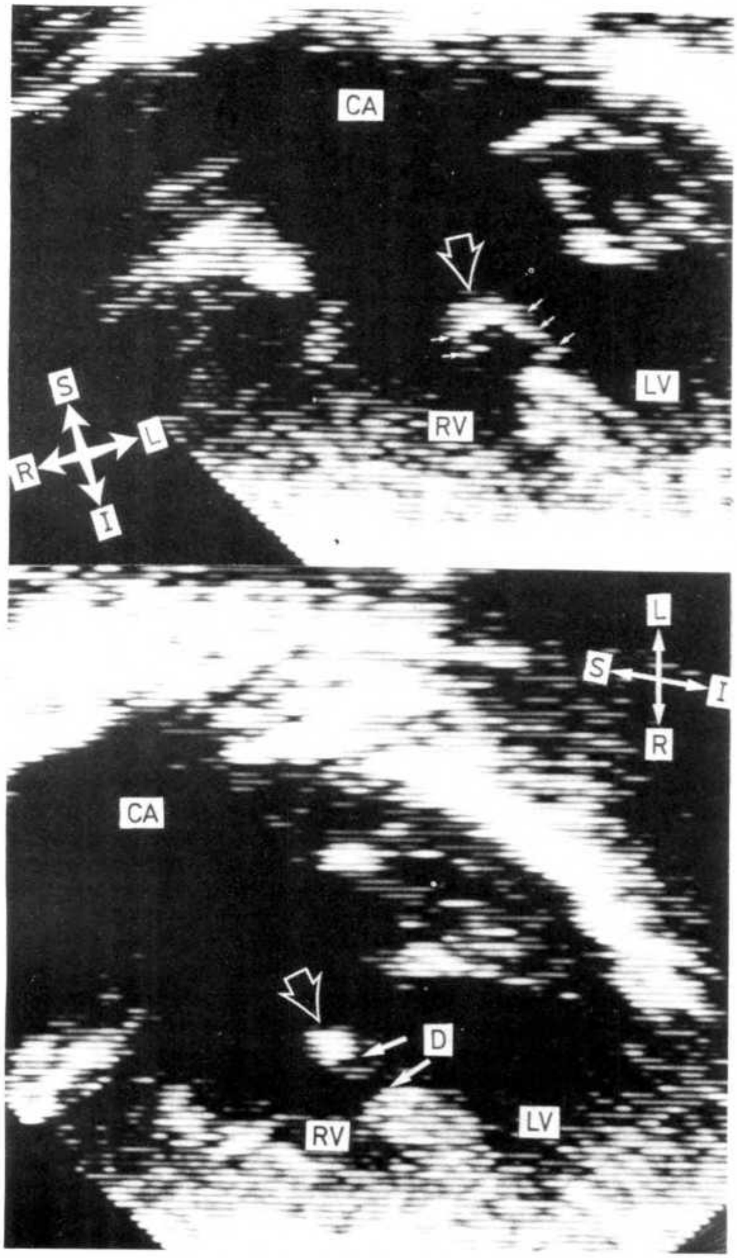

Fig. 6 *The upper picture is an apical four chamber cut in a case with partitioned orifices and a ventricular component. The small arrows indicate the medial components of the right and left sided atrioventricular leaflets. The lower picture shows the ventricular component indicated by arrows. A dense echo (hollow arrow) between the atrium and the tip of the interventricular septum represents a strand of tissue joining the anterior and posterior bridging leaflets. D, defect. See Figs. 1 and 2 for remaining abbreviations.*

seen in all cases pointing towards the interventricular septum. One patient had an additional "true" cleft in the anterior bridging leaflet which was confirmed at operation.

ASSOCIATED ABNORMALITIES IN ENTIRE GROUP OF PATIENTS

In 90 patients the atrioventricular junction was judged to be of balanced type.[10] Three cases had a dominant left and three a dominant right ventricle (Table 2) (Fig. 10). The arterial connections were concordant in 83, discordant in six, double outlet right ventricle in three, and single outlet aorta from the left ventricle in four (Table 2). Four cases had valvular pulmonary stenosis, four had pulmonary atresia, and a further two had both infundibular and valvular pulmonary stenosis.

In one patient a discrete subaortic membrane was

Table 2 *Associated defects in whole group*

VA connections	Concordant	83 (87%)
	Discordant	6 (6%)
	DORV	3 (3%)
	Single outlet (aorta from RV)	4 (4%)
AV junction	Balanced	90 (94%)
	Dominant RV	3 (3%)
	Dominant LV	3 (3%)
RVOT	Normal	86 (90%)
	Valvular PS	4 (4%)
	Pulmonary atresia	4 (4%)
	Infundibular + valvular PS	2 (2%)
TAPVD		6 (6%)
Interrupted IVC		6 (6%)
Muscular VSD		3 (3%)
Subaortic stenosis		1 (1%)

AV, atrioventricular; DORV, double outlet right ventricle; IVC, inferior vena cavae; LV, left venricle; PS, pulmonary stenosis; RV, right ventricle; RVOT, right ventricular outflow tract; TAPVD, total anomalous pulmonary venous drainage; VA, ventriculoarterial; VSD, ventricular septal defect.

visualised before operation by two dimensional echocardiography. Six patients had associated total anomalous pulmonary venous drainage and another six had an interrupted inferior vena cava. Three cases had an associated muscular ventricular septal defect. In two there was also a defect under the anterior bridging leaflet and in the other the leaflets were firmly attached to the crest of the septum.

Discussion

Of all the regions of the heart, the atrioventricular junction is the most amenable to study by two dimensional echocardiography. It is hardly surprising, therefore, that the technique provides a most reliable means of detailed and precise definition of atrioventricular septal defects. M-mode echocardiography has been of some value in diagnosing the presence of an atrioventricular septal defect,[11] particularly from the subcostal approach, but further morphological confirmation of the type of defect has been difficult and the visualisation of ventricular septal defects impossible in many cases.[12] Hagler *et al.*[1] studied a group of patients with atrioventricular defects by two dimensional echocardiography and used Rastelli's classification. They found some overlap between types A and B, with type C having a distinct pattern. In that study, however, no attention was paid to assessing the posterior bridging leaflet.

Echocardiographically the anterior bridging leaflet is best visualised in a precordial four chamber cut (Fig. 1). In this view both the leaflet and its chordal insertions are well seen, along with any potential ventricular communication lying beneath.

The posterior bridging leaflet, on the other hand, is best viewed using the subcostal cut. In a four chamber view the crux of the heart and the attachment of the posterior bridging leaflet at this point can be seen (Fig. 2). The posterior bridging leaflet can be further assessed by clockwise rotation of the transducer, to a view where the left ventricle is seen in a long axis. In this position both the anterior and posterior bridging leaflets can be seen. The anterior leaflet is seen at its attachment to the left ventricular outflow tract and the posterior leaflet along the interventricular septum (Fig. 3). The defect beneath the posterior bridging leaflet exists either between long chordae or under its free edge (Fig. 9).

The morphological hallmarks of an atrioventricular septal defect are fivefold.[5 6] Firstly, the atrioventricular junction, instead of being pinched in between the tricuspid and mitral valves (as normally occurs), is "sprung".[13] Secondly, and as a result, the muscular atrioventricular septum is missing, causing the crest of the septum to be scooped out. Thirdly, the aortic valve, instead of being wedged between the aortic and mitral valves, sits in front of the sprung atrioventricular junction in a cottage loaf or snowman fashion. Fourthly, as a result of the last two, there is inlet/outlet disproportion.[14] Finally, because of the sprung atrioventricular junction and absence of the muscular atrioventricular septum, the morphology of the left and right atrioventricular valves cannot be compared with normal mitral and tricuspid valves. The anterosuperior "tricuspid" leaflet and left and right mural leaflets are confined to one ventricle. In contrast, the two remaining bridging leaflets extend between a left ventricular and right ventricular papillary muscle. As such, they have a foot in both ventricles, the leaflets themselves crossing the septum, albeit sometimes only to a limited extent, and in other cases being firmly adherent to the septum at the crossing point.

This last point is particularly well illustrated by the cross-section echocardiographic appearances, since there is a continuous spectrum of attachment of the posterior and anterior bridging leaflets. This spectrum is illustrated for the anterior bridging leaflet in Figs. 1, 4, 7, and 8. At one end of the spectrum there is minimal bridging with the leaflet tissue firmly adherent to the septum. Next comes more bridging with firm adherence. There follows, instead of adherence, attachment by chordae which are so tightly packed that any potential interventricular defect is effectively sealed. In these patients, dense echoes persist between leaflet tissue and septal crest throughout systole and diastole. Then the chordae become wider spaced, so that a ventricular septal defect exists in the interchordal spaces (Rastelli type A). Under these circumstances, the chordae appear long and thin. The commissure thereafter moves rightward so that it is first anchored to the right side of the septum (Rastelli

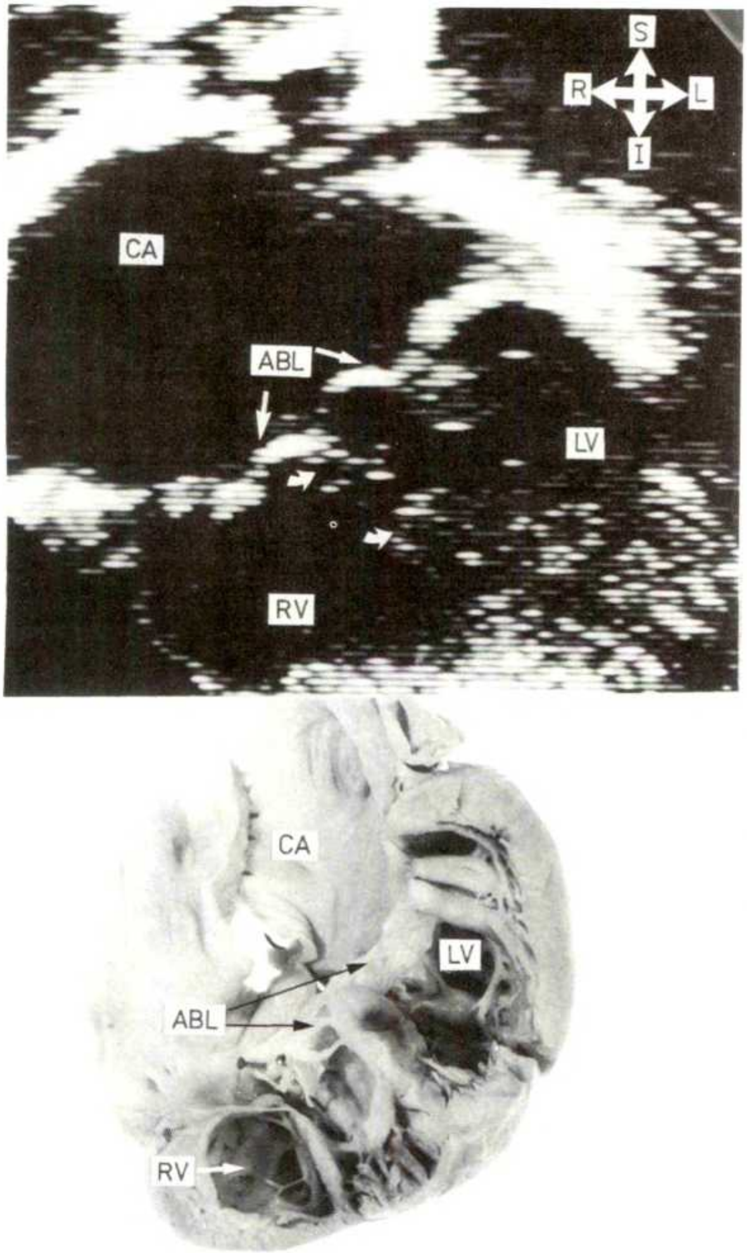

Fig. 7 *The upper picture is an apical four chamber cut in a case with common atrioventricular orifice. The anterior bridging leaflet has chordae inserted into the crest of the interventricular septum, dividing it into left and right components. The ventricular septal defect is indicated by the two arrows. The lower picture is a specimen demonstrating the chordal attachments of the anterior bridging leaflet to the interventricular septum. Note the long thin chordae tethering it to the septum. See Figs. 1 and 2 for abbreviations.*

type B) and finally to the free wall of the right ventricle (Rastelli type C). As the commissure has moved to the right, the anterior bridging leaflet appears to float free above the septum. Similar, but quite independent, variations in attachment of the posterior bridging leaflet occur. An additional spectrum may also be observed with respect to continuity of the anterior and posterior bridging leaflets. It is the existence of these separate spectra which has caused problems in classification of atrioventricular defects. Two quite separate traditions have existed in the past as to how to divide atrioventricular defects into complete and partial forms. In the first[15 16] attention has been focused on whether there is interventricular communication between the bridging leaflets and the septal crest or not. In the second[17 18] the arbiter has been

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whether or not the common atrioventricular junction is itself separated into two valve orifices. If a common atrioventricular orifice were always associated with a ventricular component beneath the bridging leaflets, and partitioned orifices were never associated with such defects, there would be no problem. The first category would be complete defects and the second would be partial defects. But this is not what is observed. The concept of transitional forms was introduced to deal with exceptions to the above rule. It has not always been appreciated, however, that two quite distinct transitional forms result. In the first, though the orifices are partitioned, there is a ventricular defect between the fused anterior and posterior bridging leaflets and the septal crest.[16] Four patients showed this abnormality. An ostium primum septal defect and ventricular component were identified, separated by a strand of tissue into which the atrioventricular leaflets were inserted (Fig. 8). This strand we interpret as the tongue of tissue providing fibrous continuity between the anterior and posterior bridging leaflets. In the second, though there is no continuity between anterior and posterior bridging leaflets, neither is there any defect between them and the septal crest.[4 17] This type of transitional form might well be impossible to recognise by two dimensional echocardiography. The anterior and posterior bridging leaflets would be seen to adhere firmly to the septal crest, but difficulty could arise in determining whether there was a small gap between them floored by the bare ventricular septal crest (that is a common orifice) or whether they were in continuity (that is partitioned).

Ventricular size depends on the degree and level of

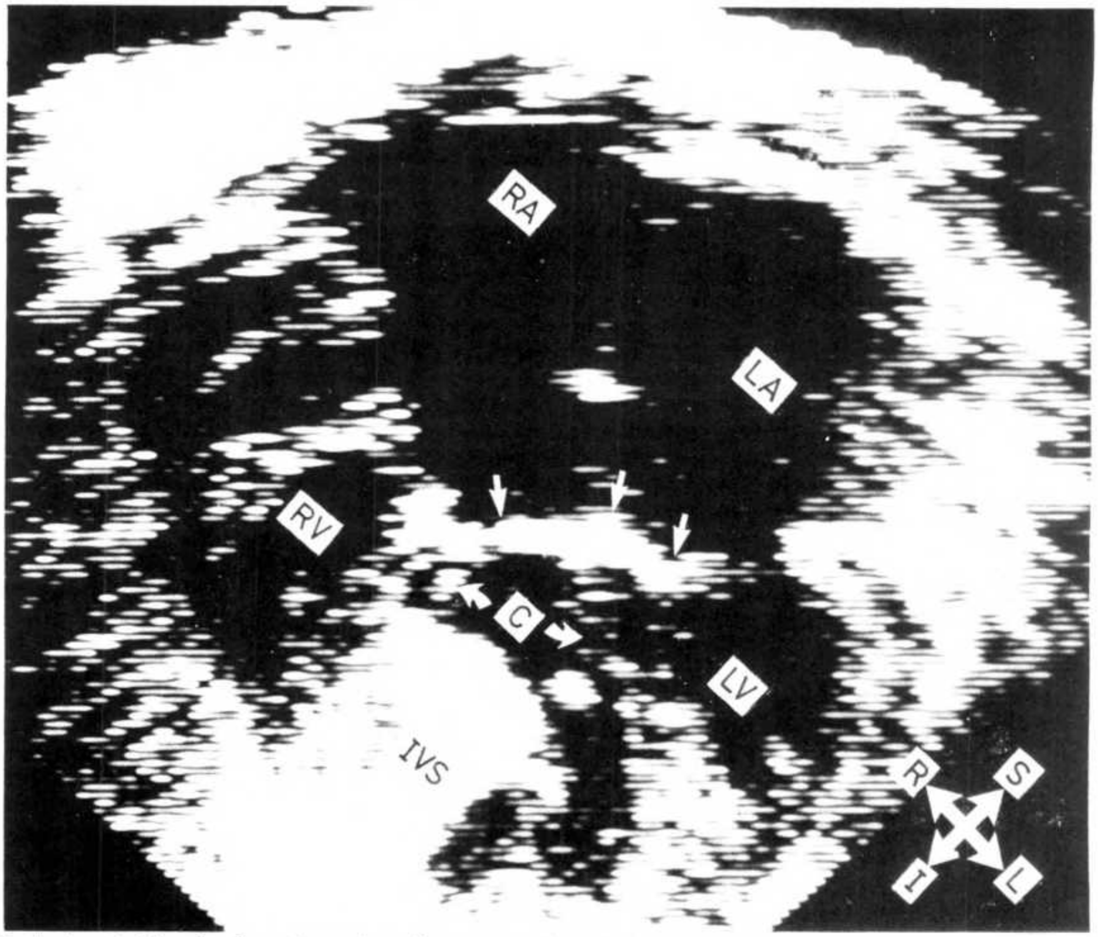

Fig. 8 *An apical four chamber cut in a patient with a common atrioventricular orifice where the chordae from the anterior bridging leaflet, indicated by the arrows, are attached to the right side of the interventricular septum. C, chordae; IVS, interventricular septum. For remaining abbreviations see Fig. 1.*

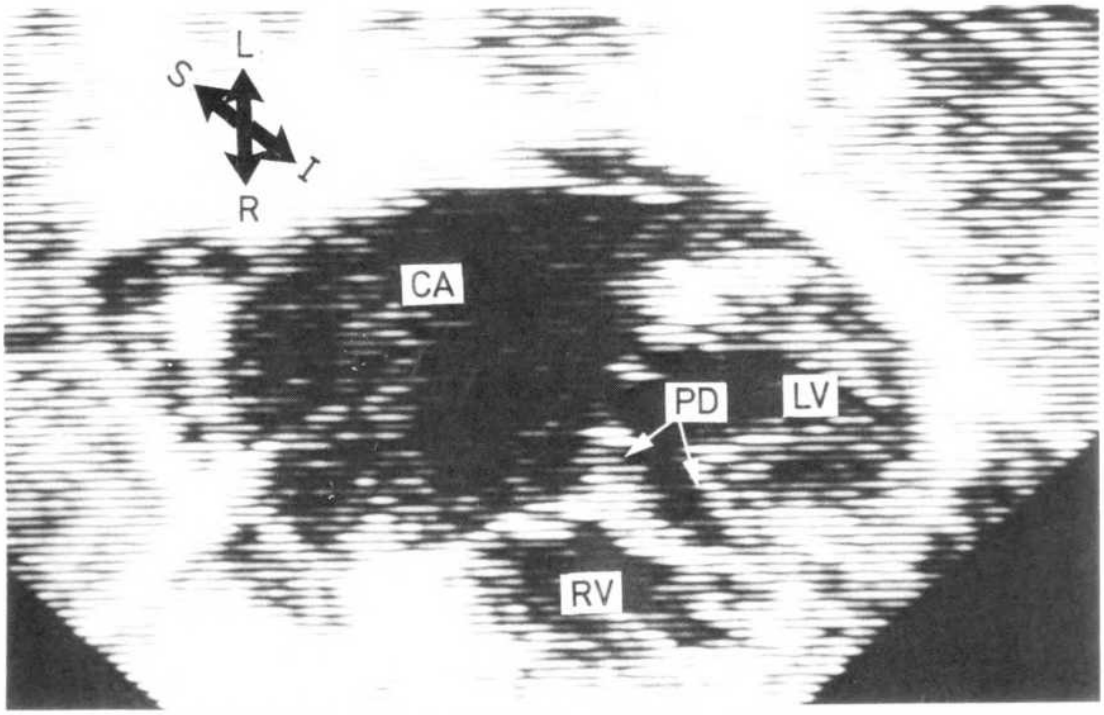

Fig. 9 *A subcostal four chamber cut with a posterior ventricular septal defect. Note the defect beneath the posterior bridging leaflet indicated by the arrows. PD, posterior defect. For remaining abbreviations see Figs. 1 and 2.*

shunting, as well as atrioventricular incompetence.[19-21] Our echocardiographic observations, however, support in qualitative fashion the original pathological observation of Bharati and Lev[10] that hearts exist in which the degree of right or left ventricular dominance cannot readily be explained on haemodynamic grounds (Fig. 9). Five of the patients described had this pattern of ventricular dominance. The distinction between this entity and univentricular hearts with common atrioventricular orifice has been discussed in detail elsewhere.[7] In brief, we believe that the normal alignment of the atrial and ventricular septa is preserved in hearts with ventricular dominance and lost in univentricular hearts, though this is a subject requiring more detailed correlation between anatomical and echocardiographic findings.

From the echocardiographic point of view, what then are the features common to all atrioventricular septal defects? In all but a few cases either an ostium primum defect or common atrium was present. Independent of the type of defect, the level of leaflet tissue on either side of the septum is the same, reflecting the absence of the muscular atrioventricular septum. In the majority of cases, independent of whether they have a partitioned or non-partitioned orifice, the left sided atrioventricular valve has a tri-leaflet appearance,[22] but with the division between the two components of the bridging leaflets unsupported by a papillary muscle. It is this division which is usually termed the "cleft", being readily recognised in the short axis section "pointing" towards the interventricular septum. This "cleft" is different from the isolated cleft seen in those with a normal anterior or aortic mitral valve leaflet.

With the advent of such precise non-invasive information regarding the anterior bridging leaflet and its attachments plus the presence or absence of an anterior defect and other associated anomalies, one may question the need for angiocardiography in cases where the anatomy is clear. The combination of clinical assessment together with pulsed Doppler demonstration of left and/or right atrial flow patterns probably provides adequate information about the degree of mitral regurgitation.

Until a non-invasive technique is developed which can reliably determine pulmonary artery pressure or vascular resistance, cardiac catheterisation will remain essential in older patients in whom pulmonary vascular disease is suspected. In infants in intractable heart failure, however, the decision to operate is based upon

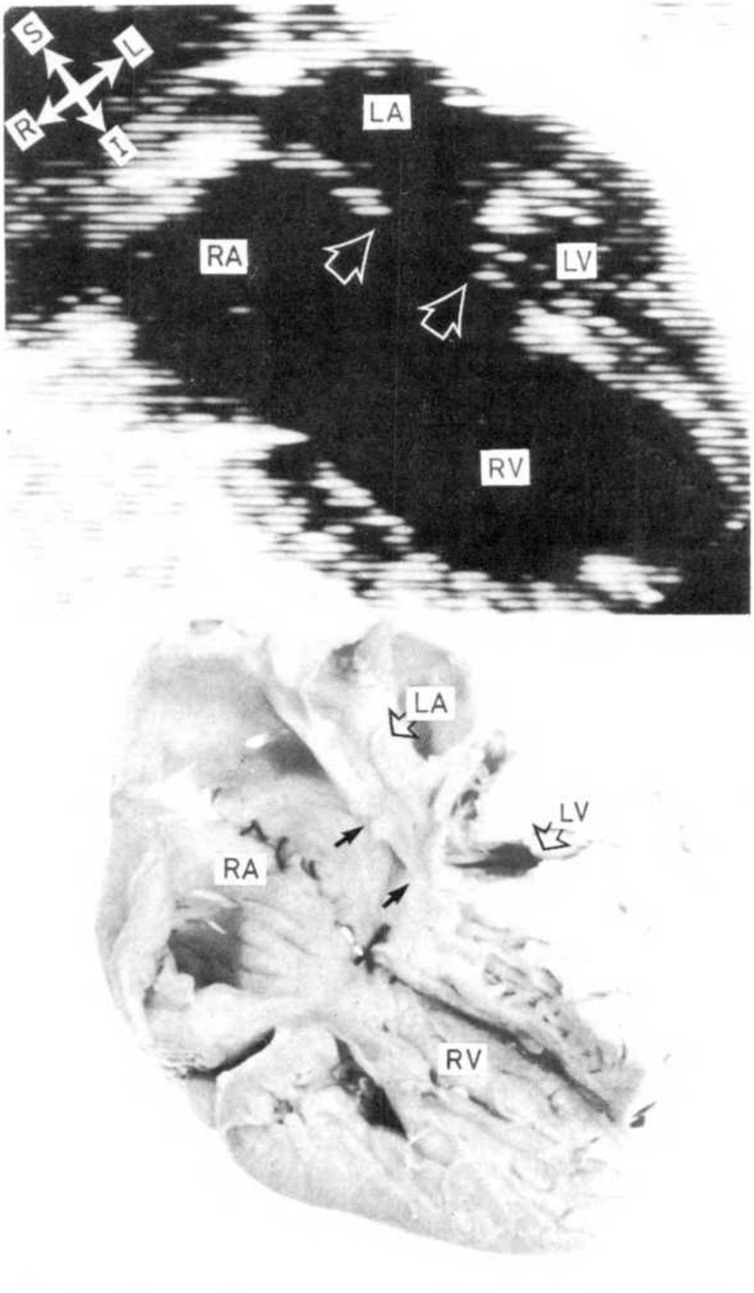

Fig. 10 *The upper panel is an apical four chamber cut in a case with an atrioventricular septal defect and a dominant right ventricle. The ostium primum defect is indicated by the large arrows. The lower panel is a specimen from a case with an atrioventricular septal defect and a dominant right ventricle. The ostium primum defect is indicated by the arrows. See Fig. 1 for abbreviations.*

their clinical status, and we have operated on a number of such patients without prior cardiac catheterisation.

It therefore appears that in depth morphological information of the type of atrioventricular septal defect can be obtained with this technique and that visualisation of a significant ventricular component under the anterior bridging leaflet is possible in all cases. Defects under the posterior bridging leaflet can be visualised in most cases. If, however, the ventricular communication exists in between thickened short chordae, then visualisation of either anterior or posterior defect is unlikely by this technique.

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Mode of inheritance of hypertrophic cardiomyopathy in Iceland
Echocardiographic study

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SUMMARY We used an abnormally thick interventricular septum ($\geqslant 1{\cdot}3$ cm) as an echocardiographic marker to find the inheritance pattern of hypertrophic cardiomyopathy among relatives of eight patients who had that disease at necropsy. Forty normal subjects served as a control group. Fifty-eight family members were examined and 18 (41%) of the 44 first degree relatives had hypertrophic cardiomyopathy. The overall inheritance pattern was consistent with an autosomal dominant genetic disorder and in one family a recessive trait could be excluded.

The diagnosis of hypertrophic cardiomyopathy can be difficult clinically as only 13% of our patients had serious symptoms and only 30% had abnormal auscultatory findings. The electrocardiogram is a useful screening test among relatives as it was abnormal in 20 (87%) of those who had an abnormally thick septum. Symmetric septal hypertrophy was found in 30% of patients with cardiomyopathy in this study and only 17% had clinical evidence of obstruction.

In a recent study in Iceland,[1] 11 patients were found to have died with hypertrophic cardiomyopathy during the years 1966 to 1977. The total Icelandic necropsy rate was 33·6% during this period and the authors estimated that 0·17% of all deceased had hypertrophic cardiomyopathy. Less than half had an obvious family history of the disease and only three had been correctly diagnosed before death.

Hence, accessible relatives of eight of these 11 patients were studied to examine the inheritance pattern of hypertrophic cardiomyopathy. An abnormally thick interventricular septum, determined by echocardiography, was used as a disease marker, excluding patients who had another recognisable cause for interventricular septal hypertrophy. We also examined how many relatives were symptomatic and to what extent physical examination and electrocardiography are helpful in the diagnosis of the disease.

Patients and methods

First degree relatives (parents, sibs, children) of eight patients of 11 who died with hypertrophic cardiomyopathy during the years 1966 to 1977 were examined. The relatives of three patients were excluded from this study since most of them were living in remote parts of the country and were unavailable for study. Forty-nine first degree relatives were alive and 44 (90%) of them were seen. Two patients were cousins and four of their common second degree relatives (aunts, uncles, grandparents) were seen, but three were unable to come.

In another case where neither parent of the proband appeared to be affected, 10 of 11 second degree relatives were examined so that the inheritable nature of the disease could be verified in this family. Altogether, the group consisted of 58 subjects, 28 men, mean age 42 years (14 to 83 years) and 30 women, mean age 44 years (6 to 82 years).

Forty healthy subjects served as a control group, 20 male and 20 female, mean age 43 years (6 to 71), most of them members of the Reykjavik City Hospital staff. None of these had hypertension, or heart or lung disease. In all, physical examination and electrocardiogram were normal and no close relative had died suddenly or unexpectedly in young or middle age. The echocardiographic results in this group were considered to be normal.

Echocardiograms were obtained with a Picker Echoview System 80C machine with a 2·5 megaHertz

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transducer and recorded on light sensitive paper (Kodak lineagraph direct print paper) with a simultaneous electrocardiogram. The transducer was positioned on the third or fourth intercostal space along the left sternal border with the subject in a supine position and when necessary rotated into a left lateral position. Standard techniques were used to obtain a satisfactory echocardiogram.[2] Interventricular septal thickness was measured from the right to the left endocardial surface, just below the tip of the mitral valve at the onset of the electrocardiographic QRS complex. Left ventricular posterior wall thickness, from the endocardial to the epicardial surface, was measured just below the posterior mitral leaflet at the same time in the cardiac cycle. The interventricular septum and left ventricular posterior wall were preferably visualised simultaneously, though this was not always possible. Systolic anterior motion of the mitral valve was looked for in the mitral plane. A switched gain circuit was used to separate chordal structures from the endocardium and to distinguish the epipericardial interphase. Measurements were carried out independently by two observers and without knowledge of the clinical data. At least two measurements were done for the interventricular septum and left ventricular posterior wall, and the mean was calculated to the nearest millimetre. The echocardiograms were reviewed jointly when interobserver difference was greater than 1 mm and the final measurement was agreed on or the mean calculated. There was no disagreement for ventricular thickness measurements in the range of 1·2 to 1·4 cm, but up to 3 mm difference was noted in two cases. In both instances interventricular septal thickness exceeded 1·6 cm.

Symptoms known to be associated with hypertrophic cardiomyopathy were specifically sought.[3 4] Previous illness, hypertension, and drug usage were noted. A physical examination was carried out, and phonocardiography, carotid pulse recording, and apexcardiography performed if considered necessary by a cardiologist. A chest *x*-ray film was taken if the cardiac impulse was felt outside the midclavicular line. Heart murmurs were graded 1 to 6 according to intensity and it was noted how systolic murmurs changed with the Valsalva manoeuvre. Innocent murmurs were judged as by Perloff.[5] Third and fourth heart sounds were confirmed by two doctors and/or by phonocardiography.

Standard 12 lead electrocardiograms were performed in the supine position. Left ventricular hypertrophy was diagnosed using the Romhilt-Estes point score system[6] and Sokolow's criteria.[7] Left atrial enlargement was defined as by Morris *et al.*[8] and right ventricular hypertrophy as by Milnor.[9] Right and left bundle-branch block, left anterior hemiblock, intraventricular conduction defects, and abnormal Q waves were defined using the criteria outlined by Friedman.[10]

Standard methods (Student's t test, χ^2, correlation coefficient) were used for statistical analysis.

Results

Among the healthy subjects the interventricular septal thickness ranged between 0·6 and 1·2 cm. We therefore distinguished between relatives who had a normal interventricular septum ($\leq$1·2 cm) (group A, 33 subjects) and 23 subjects with a thickened interventricular septum ($\geq$1·3 cm), group B. Eighteen of these were first degree relatives. In group B, 17 were men and six were women. The mean age was 50 years (18 to 83 years). Two patients were excluded from group B as they had another possible cause for septal thickening. One is an athlete[11] (interventricular septum=1·3 cm, left ventricular posterior wall=1·2 cm) and the other (interventricular septum=1·3 cm, left ventricular posterior wall=1·3 cm) had undergone cardiac catheterisation (1976), showing an abnormal aortic valve. Medical history and physical examination in group B did not suggest valvular heart disease, ischaemic heart disease, or cor pulmonale. One patient in the group, however, had a history of mild hypertension a few years earlier, but he had pronounced asymmetrical septal hypertrophy (interventricular septum=2·4 cm, left ventricular posterior wall=1·4 cm). All those in group B are therefore thought to have unexplained interventricular septal thickening or hypertrophic cardiomyopathy.

Fig. 1 shows the echocardiographic results for interventricular septum and left ventricular posterior wall thickness measurements and their ratio among subjects in the control group and groups A and B. The mean values ± 1 SD for these measurements are listed in Table 1. The difference in left ventricular wall thickness between controls and group A was not significant. The mean left ventricular posterior wall thickness was significantly greater ($p<0·01$) in group B compared with the others and so was the interventricular septum/left ventricular posterior wall ratio ($p<0·01$).

Fig. 2 shows that the interventricular septal thickness was positively associated with age among the patients with hypertrophic cardiomyopathy ($r=0·40$). No significant correlation was found in the control group, though the interventricular septal thickness did tend to increase with age ($r=0·19$). This tendency was completely lacking in group A ($r=-0·06$) possibly because three individuals, all age 16, had an interventricular septal thickness of 1·2 cm. The left ventricular posterior wall thickness tended to increase with age in the control group ($r=0·19$) and group B

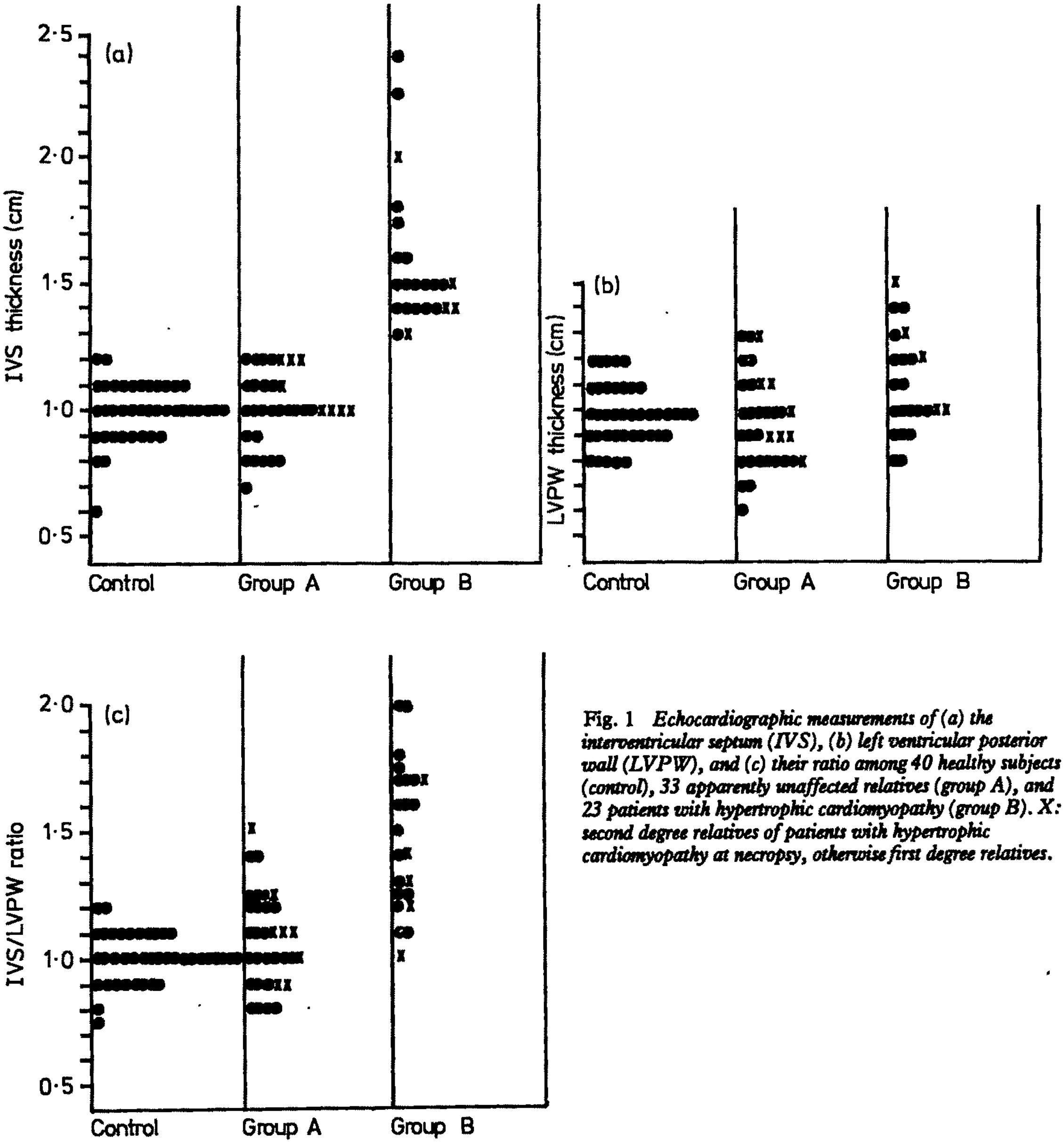

Fig. 1 *Echocardiographic measurements of (a) the interventricular septum (IVS), (b) left ventricular posterior wall (LVPW), and (c) their ratio among 40 healthy subjects (control), 33 apparently unaffected relatives (group A), and 23 patients with hypertrophic cardiomyopathy (group B). X: second degree relatives of patients with hypertrophic cardiomyopathy at necropsy, otherwise first degree relatives.*

(r=0·12) but not group A (r=0·03). These correlations were not significant.

Systolic anterior motion of the mitral valve was noted in three subjects in group B and not at all in others. A minimal mitral valve prolapse was noted in two subjects in each group of relatives.

Eighteen (41%) of the 44 first degree relatives who were examined had hypertrophic cardiomyopathy as defined and Fig. 3 shows the pedigrees of the eight probands. We applied a method[12] for assessing statistically the agreement of the observed versus expected number of cases within a family, assuming a given mode of inheritance. In six of our families the proband had a sib who was available for examination and the analysis is set out in Table 2, assuming autosomal dominant inheritance. There is an excellent agree-

Table 1 *Mean values in cm ± 1 SD for interventricular septal (IVS) and left ventricular posterior wall (LVPW) thickness measurements and their ratio in control group, and group A and B.*

	No.	*IVS thickness (cm)*	*LVPW thickness (cm)*	*IVS/LVPW ratio*
Control	40	1·00±0·12	0·99±0·12	1·00±0·10
Group A	33	1·01±0·14	0·95±0·18	1·07±0·18
Group B	23	1·58±0·29	1·10±0·19	1·48±0·29

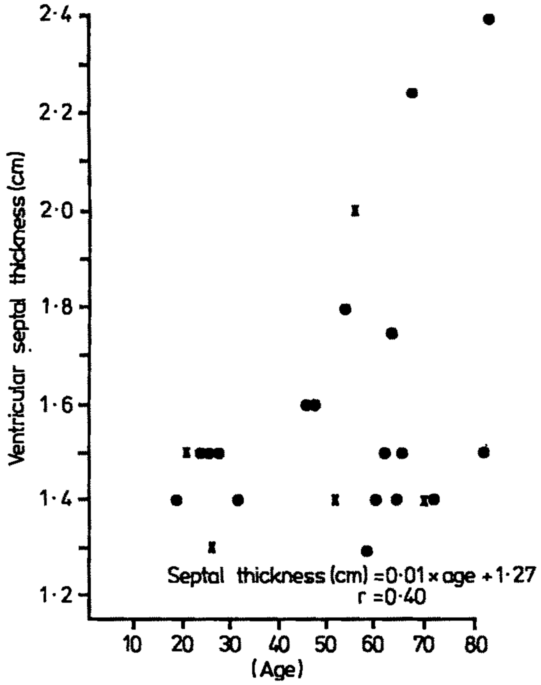

Fig. 2 *The correlation between septal thickness and age in 23 patients with hypertrophic cardiomyopathy. X: as in Fig. 1.*

ment between the observed and expected number of affected subjects in these families and the difference was not significant.

Although the parents of III2 (family 5, Fig. 3) were apparently normal, the father had an interventricular septal thickness of 1·2 cm (left ventricular posterior wall=1·3 cm) which may be inappropriate for a 25-year-old. Several other members of his family had hypertrophic cardiomyopathy. It is therefore quite possible that he has the disease. Both patients (family 2 III2 and family 3 II1, Fig. 3) who did not have an available sib had a father with the disease. We therefore conclude that the inheritance pattern of the disease is compatible with an autosomal dominant mode in these families, though the penetrance may be incomplete (family 5 II1, Fig. 3). The couple I1, I2 (family 5) are both affected (I1 interventricular septum/left ventricular posterior wall 2·0 cm/1·2 cm, I2 1·4 cm/1·0 cm). This has been confirmed further as I1 has two sisters who could be examined and one of them has septal thickening. Nine sibs of I2 were examined and three of her brothers have septal thickening. The disease is not evident in II1, II3, II5, II6, which apparently excludes the possibility of a recessive mode of inheritance in this family.

Table 3 shows the symptoms among subjects in groups A and B. Two patients in group A had chronic obstructive lung disease and one had ischaemic heart disease. One subject had a history of syncope and complained about palpitation, but no cause was identified. Less than half of the patients in group B were symptomatic and four of them had only vague symptoms like palpitation or a single syncopal attack. Older patients tended to be more symptomatic; 10 of 14 patients above the age of 50 were symptomatic while only two of nine younger patients were symptomatic. A history of hypertension was only elicited in the aforementioned patient in group B. One patient in group A was receiving drugs for hypertension. Two patients in group B were hypertensive on examination (62 year old man, 170/95 mmHg and a 71 year old woman, 170/100 mmHg) but this was not considered important because the blood pressure was only measured once and both had been normotensive previously. Auscultatory findings are shown in Table 4. Three patients had a characteristic systolic ejection murmur, grade 3 to 4 which was accentuated during the Valsalva manoeuvre and a fourth had a similar murmur that did not change with the Valsalva manoeuvre. Diastolic murmurs were not heard. Six patients had a detectable fourth heart sound and one of them had a third heart sound also. Altogether seven patients had abnormal auscultatory findings. Three of those who had a characteristic systolic murmur had an abnormal atrial impulse which was normal in others. The carotid pulse tracing was within normal limits in all instances when recorded. Chest x-ray film showed a slightly enlarged left ventricle in two patients in group B.

Twenty of the 23 who were considered to have hypertrophic cardiomyopathy had an abnormal electrocardiogram (87%) (Table 5). Two patients in group B had both criteria for left ventricular hypertrophy so that altogether 14 patients had electrocardiographic left ventricular hypertrophy (61%). There was, however, no association between left ventricular hypertrophy seen on the electrocardiogram and age or septal thickness as judged by echocardiography. Neither was such an association found among those who had Q waves on the electrocardiogram. In group A there were three subjects with incomplete right bundle-branch block and one with abnormal Q waves

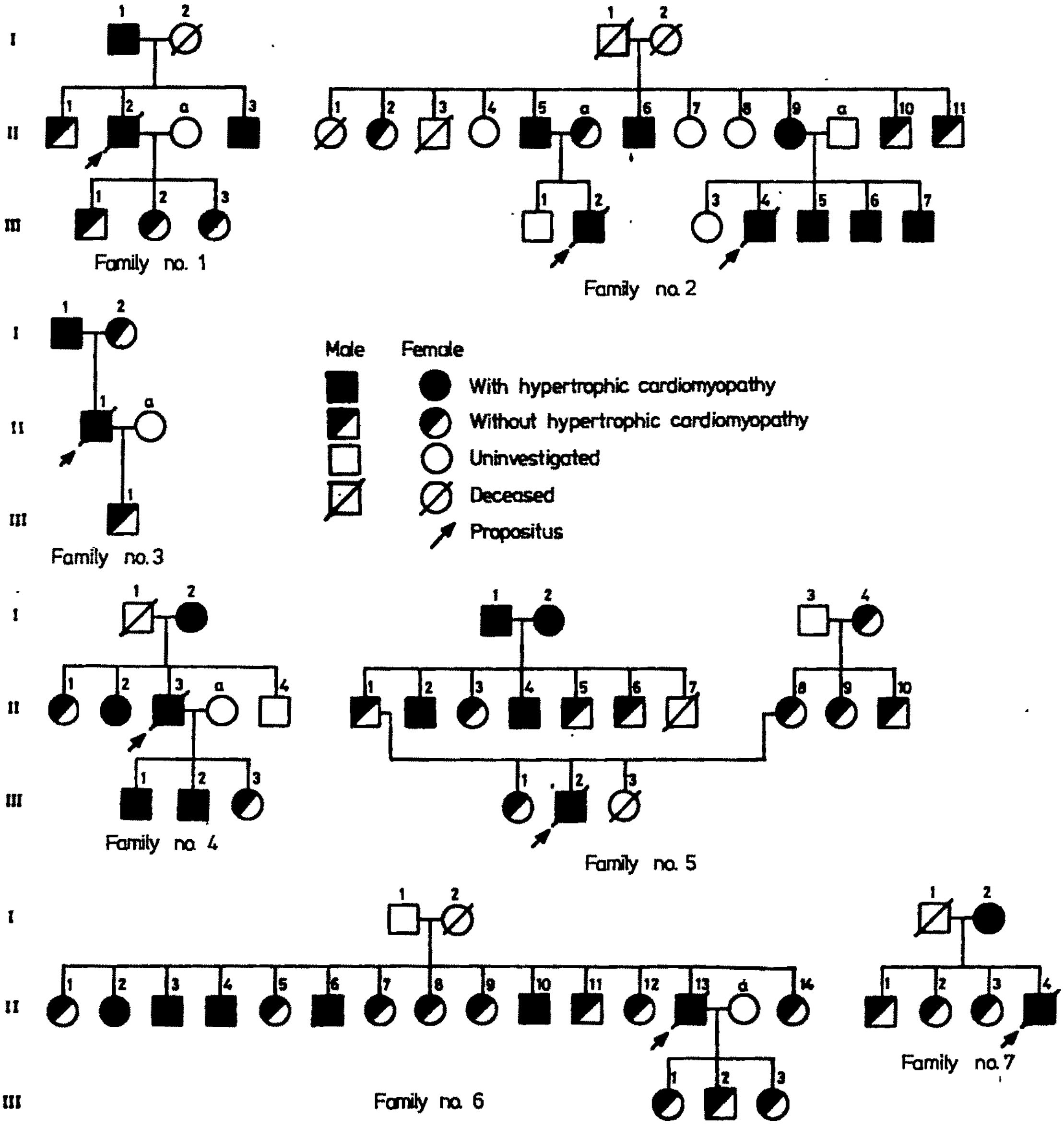

Fig. 3 *The pedigrees of eight patients who died with hypertrophic cardiomyopathy.*

but he had suffered a myocardial infarction a few years previously.

Discussion

No single echocardiographic feature is pathognomic for hypertrophic cardiomyopathy.[13–16] Doi *et al.*[15] have shown, however, that interventricular septal thickening of 1·3 cm or more has the highest combined sensitivity (83%) and specificity (94%) when differentiating between hypertrophic cardiomyopathy, as verified by cardiac catheterisation, and a normal state. Clearly, no single figure for interventricular septal thickening will completely differentiate all patients with hypertrophic cardiomyopathy from normals. In addition, in view of the septal thick-

Table 2 *Statistical analysis*[12], *in six families with hypertrophic cardiomyopathy, assuming autosomal dominant inheritance: number of observed versus expected affected cases did not differ significantly*

No. of sibs	*No. of families*	*Obs. no. of affected*	*Expected no. of affected*	*Variance*
2	1	1	1·333	0·222
3	2	4	3·428	0·980
4	2	5	4·166	1·564
14	1	6	7·000	3·497
	6	16	15·927	6·263

Table 3 *Symptoms among 56 family members of patients who died with hypertrophic cardiomyopathy*

	Group A total no. 33	*Group B total no. 23*
Effort dyspnoea	2 (6%)	7 (30%)
Angina pectoris	1 (3%)	3 (13%)
Palpitation	1 (3%)	7 (30%)
Dizziness	0	1 (4%)
Syncope	1 (6%)	2 (9%)
Fatigue	1 (3%)	2 (9%)
Without symptoms	28 (85%)	12 (52%)

Table 4 *Auscultatory findings in groups A and B*

	Group A	*Group B*
Innocent systolic murmurs	9 (27%)	7 (30%)
Characteristic systolic murmur	0	4 (17%)
Third heart sound	0	1 (4%)
Fourth heart sound	0	6 (26%)

Table 5 *Electrocardiographic abnormalities in groups A and B*

		Group A total 33	*Group B total 23*
Left ventricular hypertrophy	Sokoloff	2 (6%)	9 (39%)
	Romhilt-Estes		7 (30%)
Right ventricular hypertrophy			1 (4%)
Left atrial abnormality			5 (20%)
Abnormal Q waves		1 (3%)	4 (17%)
Right bundle-branch block		3 (9%)	
Left anterior hemiblock			1 (4%)
Intraventricular conduction defect			2 (9%)
P—Q >0·20 s			4 (17%)
q—Tc >0·43 s			2 (9%)
Total		4 (12%)	20 (87%)

ening which apparently may occur with age, some young normal subjects as well as older patients with hypertrophic cardiomyopathy may be incorrectly classified.

Gardin *et al.*[17] suggested that the occasional normal subject above the age of 45 will have an interventricular septal thickness of 1·3 cm and that even 1·4 cm around 80 years of age may be normal. Doi *et al.*[15] reported that two of their 36 normal subjects had an interventricular septal thickness of 1·3 cm, but they did not state their age. All our patients above the age of 50 who had an interventricular septal thickness of 1·3 to 1·4 cm also had abnormal electrocardiograms, which supports the opinion that they do indeed have hypertrophic cardiomyopathy. In fact such patients (interventricular septum=1·3 to 1·4 cm) may die suddenly and unexpectedly.[18]

The most common cause of interventricular septal hypertrophy, that is hypertension, was noticeably rare in our subjects, one in each group. Two patients (Fig. 3, family number 4 II4 and number 5 III3), whom we did not examine, had a ventricular septal defect but other cases of cardiovascular malformations were not suspected clinically in our group of relatives.

Seven (30%) of our group B patients had symmetrical rather than asymmetrical septal hypertrophy. Two of them had an interventricular septum/left ventricular posterior wall ratio of 1·25. The remaining five had a ratio of 1·4/1·3, 1·5/1·4, 1·4/1·5, 1·4/1·2, and 1·4/1·3. Two of these were under 25 years of age. This may overestimate the true prevalence of symmetrical septal hypertrophy among patients with hypertrophic cardiomyopathy. Our material is small, and six other second and third degree relatives, not included in this study, had asymmetrical rather than symmetrical septal hypertrophy. From larger series it seems that the true prevalence was around 9%.[15 19]

Our results support the opinion that hypertrophic cardiomyopathy is a genetic disorder transmitted as an autosomal dominant trait with a high degree of penetrance. This is in agreement with two other studies based on echocardiography,[20 21] though other criteria were used. Only 20% of the probands' children had the disease as defined. The reason for this is probably that the mean age of the children was 21 years (range 15 to 27 years) and an interventricular septal thickness of 1·3 cm might be higher than normal in this age group. Clark *et al.*[20] used asymmetrical septal hypertrophy as a disease marker and found 30% of the probands' children to be affected. It seems that both markers are imprecise in young adults. It is still controversial how often the disease is sporadic[22] but we have in this and a previous study[1] shown that all patients who were diagnosed with hypertrophic cardiomyopathy at necropsy during a 12 year period in Iceland had a family history of this disease.

None of our patients had been diagnosed as hypertrophic cardiomyopathy before the study, though almost half were symptomatic. In previous reports 8 to 86% of patients had symptoms.[4 21] This difference can in part be accounted for by differing selection of patients and differing definition of significant symptoms. Only three (13%) of our patients, however, had consulted a physician because of their illness and the bedside diagnosis was obviously difficult as only four (17%) had a systolic murmur suggesting hypertrophic cardiomyopathy with obstruction.

The electrocardiogram serves as a useful screening test for the disease among the relatives of those who die with hypertrophic cardiomyopathy as it was abnormal in 87% of those who had the disease. These abnormalities are, however, not specific. The prevalence of abnormal electrocardiographic findings among patients with hypertrophic cardiomyopathy varies in different studies, but our results are in agreement with those of Savage *et al.*[23] who reported that 73% of asymptomatic patients with non-obstructive hypertrophic cardiomyopathy and almost all of those who had left ventricular obstruction or were symptomatic had electrocardiographic changes.

Bjarnason and Hallgrimsson estimated,[1] using the rate and incidence of hypertrophic cardiomyopathy at gross necropsy, that on average 2·5 patients died each year with it in the whole of Iceland (mean population during the period was 220 000). Given an annual mortality for hypertrophic cardiomyopathy patients of 3·5%,[4 24] roughly 72 patients should have it in Iceland which constitutes a prevalence of 33/100 000. The necropsies, however, are not selected randomly. One-third of them are medicolegal and the rest hospital necropsies where patients with malignancies and heart disease tend to have priority.[25] Moreover, the necropsy rate declines with the age of the patients.[25] Any comparison between pathological prevalence data and echocardiographic findings is hampered by a lack of common criteria. Minimally affected patients are probably not recognised at necropsy. The true prevalence is therefore probably higher than the necropsy figures imply.

In conclusion, our study has confirmed earlier reports suggesting that hypertrophic cardiomyopathy is inherited in an autosomal dominant manner. Most patients with hypertrophic cardiomyopathy initially identified by echocardiography were found to have electrocardiographic abnormalities and many had cardiac symptoms on questioning.

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Cardiac work and myocardial substrate extraction in congestive cardiomyopathy

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SUMMARY Left ventricular pressure, cardiac output, coronary sinus blood flow, and myocardial substrate extraction were measured in 10 patients with congestive (dilated) cardiomyopathy and in a control group of nine patients investigated for chest pain who proved to have no angiographic or metabolic evidence of ischaemic heart disease. Haemodynamic and angiographic measurements confirmed that the patients with cardiomyopathy had severe left ventricular disease. Coronary sinus blood flow and myocardial oxygen consumption were greater in the patients with cardiomyopathy, but were similar in the two groups when normalised for ventricular mass. Efficiency, estimated from the oxygen cost of external work, was grossly reduced in the cardiomyopathy group. No major differences in substrate extraction were demonstrated between the groups. Myocardial lactate production was not observed in any patient with cardiomyopathy. Free fatty acid and glycerol release were observed in several control subjects but in none of the patients with cardiomyopathy.

Measurements were repeated during pacing in five of the cardiomyopathy group and in each of the control subjects. The latter showed a normal response to pacing, whereas of the former, four sustained increases in end-diastolic pressure, two showed large reductions in both cardiac output and coronary flow, and only one increased coronary flow during pacing. Despite the failure of coronary flow to increase, lactate extraction remained high.

These results show that anaerobic carbohydrate metabolism is not an important energy source for the myopathic heart and suggest that ischaemia does not contribute to poor left ventricular function. No gross abnormality of oxidative metabolism was identified, implying that low efficiency lay in the poor contractile performance of the myopathic heart.

Congestive, or dilated, cardiomyopathy is a descriptive diagnosis attached to those patients with a primary disorder of cardiac muscle which results in ventricular dilatation, little if any hypertrophy, and reduced ejection.[1 2] Investigation rarely yields the aetiology, and microscopical examination of endomyocardial biopsy specimens usually demonstrates non-specific muscle damage.[3 4] Microchemical analysis of biopsy material has shown conspicuously raised levels of cytosol lactate dehydrogenase,[5] though this is not a specific marker for the disease, as moderately increased concentrations are found in patients with poor ventricular function secondary to valvular disease.[5] The significance of this finding is uncertain, but because there have been occasional reports of myocardial lactate production in congestive cardiomyopathy[6 7] it has been suggested that the increased lactate dehydrogenase levels reflect the importance of anaerobic carbohydrate metabolism as an energy source for the myopathic heart.[5]

We have measured haemodynamics, coronary blood flow, and myocardial substrate extraction in 10 patients with severe congestive cardiomyopathy, and in a control group of nine patients investigated for chest pain in whom no cardiac abnormality was found. This study was undertaken to investigate the relation between cardiac work and energy consumption and to identify any abnormality of substrate extraction by the myopathic heart.

Patients and methods

Two groups of patients were studied; 10 patients who had clinical evidence of heart failure thought to result from congestive cardiomyopathy, and nine patients

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without heart failure who were under investigation for disabling chest pain. The procedure was approved by the hospital ethical committee, and each patient gave written consent.

All studies were performed in the morning after an overnight fast. Digoxin and diuretics were continued in the cardiomyopathy group until the time of study, but in the chest pain group beta-blocking drugs were stopped 48 hours beforehand. Premedication was with atropine 0·3 mg and diazepam 10 mg intramuscularly. At the same time heparin (45 units/kg) was given intravenously to minimise the effect of a subsequent dose of heparin upon free fatty acid concentrations.[8] Right and left heart catheterisation was performed via the right femoral vein and artery. Immediately after arterial catheterisation a second dose of heparin (45 units/kg) was administered. After routine pressure measurements and coronary arteriography, a Ganz catheter was advanced into the coronary sinus via a left antecubital vein, and its position confirmed by injection of contrast. Cold saline was injected into the right atrium to ensure that the dilution thermistor was unaffected by reflux of atrial blood.[9] Using the long sheath technique[10] a catheter tip micromanometer (either a Telco MM52 or No. 5 Millar) was positioned in the body of the left ventricle. In each of the nine patients with chest pain and in four of the patients with cardiomyopathy the retrograde aortic route was used, but in six patients with cardiomyopathy the catheter was positioned transseptally. Cardiac output was measured by dye dilution using a Schwarzer Swan-Ganz catheter positioned in the pulmonary artery, or (in four patients with cardiomyopathy) a CME velocity probe positioned in the ascending aorta.

No measurement were made for at least 20 minutes after coronary arteriography. Left ventricular pressure, cardiac output, and coronary sinus flow were measured, and left ventricular and coronary sinus blood were sampled. In each of the nine patients with chest pain, and in five of the cardiomyopathy group, measurements and samples were repeated during incremental coronary sinus pacing. Left ventricular cineangiography was performed at the end of the study.

The micromanometer and thermistor signals were displayed on a Cambridge 12 channel recorder, and stored on tape. Max dP/dt was derived by an electronic differentiator or by computer, and KVmax was calculated from developed pressure[11] using either an electronic processor[12] or a computer. Mean left ventricular systolic pressure was derived by planimetric integration, or, when pressure and flow signals were measured simultaneously, by computer analysis[13] Green dye curves were analysed by an IVH 3 cardiac output computer. When a velocity probe was used, cardiac output was calculated as mean flow velocity derived from integration of the velocity signal, multiplied by aortic cross-sectional area estimated by echocardiography or aortography. Coronary sinus blood flow was measured by constant infusion thermodilution.[14] Using a computer—light pen system previously described,[12] the right anterior oblique view of the left ventricular cineangiogram was analysed to yield volume, ejection fraction, and mass.

The oxygen content of heparinised blood samples was measured upon a LEX-O_2 CON TL. Blood was added to an aliquot of perchloric acid for subsequent estimation of concentrations of lactate and pyruvate,[15] hydroxybutyrate, and acetoacetate,[16] and glycerol.[17] For measurement of free fatty acids[18] blood was added to sequestrine tubes and centrifuged. All samples were immediately put on ice, and stored at −20°C.

Myocardial oxygen consumption was calculated as coronary sinus blood flow multiplied by the difference between arterial and coronary sinus oxygen content. The extraction of a substrate is the difference in concentration between arterial and coronary sinus blood (A-V), and extraction ratio, that difference expressed as a percentage of arterial concentration $\left(\frac{A-V}{A}\right)\%$. The oxygen extraction ratio of a substrate is defined as the amount of oxygen required to catabolise completely the amount of that substrate extracted expressed as a percentage of total oxygen extraction.

Myocardial efficiency was estimated using Bing's formula[19]:

$$\text{efficiency} = \frac{\text{LV minute work (kg m/min)}}{\text{Myocardial oxygen consumption (ml/min)}}\%$$

$2{\cdot}059 \times 0{\cdot}806$ (normal = 40%)

Values are expressed as mean ± standard error. Student's t test and linear regression are used where appropriate, and $p<0{\cdot}05$ is considered significant.

Results

The diagnosis of congestive cardiomyopathy was confirmed in our 10 patients. Each had a dilated, poorly contracting left ventricle, normal coronary arteriograms and, with the exception of mild subvalvar mitral regurgitation, normal cardiac valves. The aetiology of myocardial damage was not identified in any patient. Two patients (cases 3 and 8) had a history suggestive of a preceding viral illness, but this was not confirmed by serology. One patient (case 1) had been a heavy drinker for many years.

Each of the nine patients investigated for chest pain (control group) had angiographically normal coronary arteries, and did not develop angina, electrocardiographic abnormalities, or produce lactate during pacing. Basal haemodynamics and quantitative left ventricular cineangiography were normal in these patients.

BASAL HAEMODYNAMICS (Tables 1 and 2)

Basal heart rate was 99 ± 8 beats/min in the patients with cardiomyopathy and 86 ± 6 beats/min in the control subjects (NS). Cardiac index, left ventricular systolic pressure, minute work, max dP/dt, KVmax, and ejection fraction were significantly lower, and end-diastolic volume index and end-diastolic pressure significantly higher in the cardiomyopathy group than in the controls. Coronary sinus blood flow and myocardial oxygen consumption were increased in the patients with cardiomyopathy compared with the control subjects and, as their left ventricular minute work was low, calculated efficiency was grossly reduced. None of the patients with cardiomyopathy had severe hypertrophy, though end-diastolic left ventricular free wall thickness, 0·93 ± 0·06 cm, was greater than in the control subjects, 0·69 ± 0·04 cm ($p<0·05$). Because of this small increase in wall thickness and the large increases in cavity dimensions, left ventricular mass was significantly greater in the cardiomyopathy than in the control group. Coronary sinus blood flow and myocardial oxygen consumption normalised for ventricular mass were similar in the two groups.

Table 1 *Resting haemodynamics in cardiomyopathy and control group*

Case No.	*Age (y)*	*Sex*	*CI (l/min per m²)*	*LVSP (mmHg)*	*LVEDP (mmHg)*	*KVmax (s⁻¹)*	*Max dP/dt (mmHg/s)*	*LVEDVI (ml/m²)*	*EF*
Cardiomyopathy group (n = 10)									
1	46	M	1·52	84	16	80	997	218	0·25
2	49	M	1·34	97	28	89	925	228	0·24
3	18	M	0·80	72	18	94	629	310	0·02
4	38	M	1·97	84	10	40	660	171	0·20
5	61	M	1·68	90	7	69	1145	201	0·23
6	41	M	2·02	80	15	43	920	225	0·22
7	38	F	1·80	120	17	50	900	100	0·30
8	18	M	1·24	83	28	62	609	395	0·12
9	42	M	2·18	100	6	68	1200	121	0·39
10	30	M	1·33	77	23	81	579	275	0·17
Mean	38·1		1·59*	88·7*	17*	67*	856*	224*	0·21*
SEM	4·2		0·13	4·4	2·5	6	72	31	0·04
Control group (n = 9)									
Mean	46·2		3·07	124	6·3	91·8	1527	59	0·66
SEM	5·1		0·32	8	2·0	5	58	4	0·016

*$p<0·01$ when cardiomyopathy and control group are compared

CI, cardiac index; LVSP, left ventricular systolic pressure; LVEDP, left ventricular end-diastolic pressure; LVEDVI, left ventricular end-diastolic volume index; EF, ejection fraction.

Table 2 *Resting haemodynamics in cardiomyopathy and control groups*

Case No.	*CSF (ml/min)*	*MVO₂ (ml/min)*	*LVMW (kg m/min)*	*Efficiency (%)*	*LV mass (G)*	*CSF/100g (ml/min)*	*MVO₂/100g (ml/min)*
Cardiomyopathy group							
1	213	19·0	2·50	7·4	291	73	6·5
2	183	15·6	2·23	8·6	216	85	7·2
3	171	35·2	0·80	1·4	315	54	11·2
4	420	48·3	2·69	3·4	390	108	12·3
5	174	32·0	2·87	5·4	222	78	14·4
6	392	52·9	2·99	5·3	340	115	15·6
7	289	35·0	3·07	5·3	181	160	19·3
8	142	21·3	0·88	1·6	190	75	11·2
9	211	26·8	4·01	9·0	248	85	10·8
10	155	21·7	0·83	2·3	365	43	5·9
Mean	235*	30·8*	2·29*	4·8*	276*	88	11·4
SEM	31	3·9	0·35	0·9	24	11	1·3
Control group							
Mean	120	11·6	6·99	39·4	121	99	9·6
SEM	15	1·6	0·63	4·0	13	10	0·8

*<0·01 when cardiomyopathy and control group are compared

CSF, coronary sinus blood flow, MVO_2, myocardial oxygen group uptake; LVMW, left ventricular minute work, CSF/100g, coronary sinus blood flow/100g myocardium; MVO_2/100g, oxygen consumption/100g myocardium.

BASAL METABOLIC RESULTS

The arterial and coronary venous concentrations, extraction, extraction ratio, and oxygen extraction ratio of the six substrates measured are listed in Table 3.

The high mean arterial lactate concentration in the cardiomyopathy group was largely the result of concentrations of 2·705 and 1·379 mmol/l in cases 3 and 8, both of whom had a very low cardiac output. Myocardial lactate production was not observed in either group. Though lactate extraction and oxygen extraction ratio were significantly greater in the cardiomyopathy than in the control group, these differences were caused in part by greater arterial lactate concentrations. Extraction ratio did not differ significantly between the two groups.

No differences were shown between the two groups in concentrations or extraction of pyruvate, hydroxybutyrate, or acetoacetate.

Free fatty acid extraction was positive in each of the patients with cardiomyopathy, whereas two of the control subjects had negative values. Extraction and extraction ratio were significantly greater in the cardiomyopathy than in the control group and these differences were still significant when the two controls with negative values were excluded from analysis.

Glycerol extraction was positive in each of the six patients with cardiomyopathy, but glycerol release was observed in six of the nine control subjects; consequently glycerol extraction and extraction ratio were significantly greater in the cardiomyopathy group.

The total of the oxygen extraction ratios of the substrates measured was 130% ± 18 in the cardiomyopathy group and 86% ± 19 in the control group (NS).

Effects of pacing

The results at the highest pacing rate are listed in Table 4. Pacing was without effect upon end-diastolic pressure or indices of contractility in the cardiomyopathy group, whereas in the control group end-diastolic pressure decreased and max dP/dt increased significantly. Coronary flow increased in each of the control subjects, but rose substantially in only one patient with cardiomyopathy; in two it changed little, and in two it decreased. Cardiac output decreased on pacing in both the patients who sustained large reductions in coronary flow.

Myocardial lactate production was not seen in either group during pacing, even in the two patients who sustained reductions in coronary flow.

Discussion

Although all nine patients in the control group had a history of chest pain, their normal haemodynamics and coronary arteriograms, and the failure of pacing to provoke pain or myocardial lactate production allow them to be regarded as normal control subjects.

Each of the patients in the cardiomyopathy group had reached an advanced stage of their disease. Though it is likely that within the group there were

Table 3 *Basal metabolic results*

	A (*mM/l*)	*CS* (*mM/l*)	*A-V* (*mM/l*)	*A-V/A* (%)	*O_2ER* (%)
Lacate					
COCM (n = 10)	0·966±0·216	0·648±0·160	0·347±0·069	35·7±3·9	19·9±3·4
Controls (n = 9)	0·562±0·066	0·407±0·044	0·134±0·032	27·5±3·6	11·1±2·2
	NS	NS	p<0·05	NS	p<0·05
Pyruvate					
COCM (n = 8)	0·057±0·013	0·036±0·008	0·0209±0·006	32·2±7·8	1·2±0·2
Controls (n = 9)	0·044±0·010	0·036±0·009	0·0179±0·010	20·0±9·1	0·6±0·2
	NS	NS	NS	NS	NS
Hydroxybutyrate					
COCM (n = 7)	0·156±0·038	0·091±0·021	0·065±0·019	42·3±6·1	5·6±1·0
Controls (n = 9)	0·188±0·053	0·121±0·035	0·066±0·19	33·6±5·5	6·9±2·1
	NS	NS	NS	NS	NS
Acetoacetate					
COCM (n = 7)	0·105±0·025	0·053±0·028	0·052±0·017	45·1±8·7	3·8±1·6
Controls (n = 9)	0·089±0·021	0·046±0·026	0·043±0·014	42·6±3·9	3·5±0·8
	NS	NS	NS	NS	NS
Free fatty acids					
COCM (n = 9)	0·753±0·114	0·539±0·080	0·225±0·037	30·2±2·5	102±18
Controls (n = 9)	0·958±0·149	0·894±0·167	0·063±0·054	7·2±7·1	61·8±18*
	NS	NS	p<0·05	p<0·01	NS
Glycerol					
COCM (n = 6)	0·076±0·014	0·056±0·014	0·020±0·004	29·2±5·8	—
Controls (n = 9)	0·064±0·001	0·074±0·007	−0·010±0·007	−12·6±8·6	—
	NS	NS	p<0·01	p<0·01	—

Values expressed as mean ± SEM. A, arterial concentration; CS, coronary sinus concentration; NS, not significant; A-V, extraction; A-V/A, extraction ratio; O_2ER, oxygen extraction ratio.
*Excluding negative values.

Table 4 *Effects of pacing*

Case	*HR*		*LVSP*		*LVEDP*		*CO*		*Max dP/dt*		*KV max*		*CSF*		MVO_2		*LER*	
No.	*C*	*P*	*C*	*P*	*C*	*P*	*C*	*P*	*C*	*P*	*C*	*P*	*C*	*P*	*C*	*P*	*C*	*P*
Congestive cardiomyopathy																		
4	91	143	84	79	10	16	3·5	2·3	660	640	40	46	420	284	48·3	31·2	34·5	24·8
6	113	170	80	80	15	22	3·9	2·0	920	920	43	60	392	247	52·9	34·0	38·7	30·0
7	90	160	120	110	17	30	3·7	3·8	900	1300	50	56	289	320	35·0	36·9	19·0	19·0
9	90	130	100	90	6	7	4·9	4·7	1200	1170	68	64	211	217	26·8	26·0	46·7	44·2
10	76	120	77	71	23	7	2·8	3·2	579	821	81	82	155	250	21·7	32·5	40·5	38·5
Mean	92	145	92	86	14	16	3·8	3·2	852	970	56	62	293	264	36·9	32·1	35·9	31·3
SEM	5·9	9·2	8	7	3	4	0·5	0·5	109	53	8	6	51	18	6	2	4·7	4·5
			NS		NS		NS		NS		NS		NS		NS		NS	
Controls (n = 9)																		
Mean	85	154	124	108	6	3	5·8	5·3	1527	2083	92	101	121	183	11·6	20·9	27·5	22·7
SEM	8	9	8	5	2	2	0·6	0·8	58	82	5	8	15	26	1·6	3·4	3·6	4·3
			p<0·05		p<0·05		NS		p<0·01		NS		p<0·01		p<0·01		NS	

HR, heart rate; LVSP, peak left ventricular systolic pressure (mmHg);LVEDP, left ventricular end-diastolic pressure (mmHg); CSF, coronary sinus blood flow (ml/min); MVO_2, myocardial oxygen consumption (ml/min); LER, lactate extraction ratio; C, control state; P, pacing; NS, not significant.

different causes of myocardial damage, the 10 patients were haemodynamically and metabolically so similar it is legitimate to treat them as a homogeneous group.

The efficiency of the heart can be estimated by relating external work to myocardial oxygen consumption.[19] The mean value of 39% in the control group is in close agreement with previous estimates of the efficiency of the normal heart.[19] Each of the patients with cardiomyopathy had low efficiency, and their mean value of 4% emphasises the severity of the disturbance of myocardial energetics. The oxygen consumption of the ventricle is determined largely by muscle tension,[20] dependent upon both pressure and volume, while external work is determined by the extent of muscle shortening against this tension (load). Dilatation therefore increases both myocardial oxygen consumption and the load opposing shortening. When muscle function is poor, shortening against load is reduced, so efficiency will be low, and will decrease further as energy consumption and load increase with further dilatation. That the failing dilated heart operates against excessive load is suggested by the large improvement in efficiency during infusion of sodium nitroprusside.[21] Dilatation and excessive load are logical consequences of poor contractile function, and efficiency may be low when oxidative metabolism and the oxygen cost of tension development are normal.

The normal ventricle hypertrophies without dilating in response to chronic pressure overload, and the increased wall thickness maintains wall stress within normal limits.[22] When a ventricle of a given mass dilates, the increase in cavity dimensions and decreased wall thickness will increase stress, which may stimulate hypertrophy. Though none of our patients had gross hypertrophy, their end-diastolic wall thickness was greater than in the control subjects and their greater myocardial oxygen consumption was related largely to increased mass.

The normal heart derives its energy supply from the oxidation of free fatty acids, lactate, and glucose, with smaller contributions from the oxidation of pyruvate and ketone bodies.[23] The pattern of substrate extraction in both groups of patients was broadly similar to results reported for the normal heart.[23–25]

Myocardial lactate extraction was high in each of the patients with cardiomyopathy, and myocardial lactate production was not observed in either group. Lactate extraction and oxygen extraction ratio were significantly greater in the cardiomyopathy group than in controls. These differences may have been the result in part of the high arterial lactate concentrations observed in several patients in the cardiomyopathy group. In addition, the high arterial free fatty acid concentrations in several control subjects would be expected to inhibit myocardial lactate extraction.[26] The high lactate extraction in the cardiomyopathy group is consistent with the increased concentration of cytosol lactate dehydrogenase found in ventricular biopsy specimens taken from patients with this condition,[5] though comparable lactate extraction ratios are found in patients with hypertrophic obstructive cardiomyopathy[27] where levels of the enzyme are normal.[5] Moderate increases in lactate dehydrogenase have been reported in patients with poor left ventricular function secondary to chronic valvular disease.[5] The low cardiac output of severe heart failure tends to increase arterial lactate concentration, so that increased cytosol lactate dehydrogenase levels may be a nonspecific adaptation allowing the myocardium to metabolise the available lactate.

There have been occasional reports of lactate production by the myopathic heart,[6 7] and it has been suggested that anaerobic carbohydrate metabolism is an important energy source in this condition.[5] As myocardial lactate production was not observed in our patients it is unlikely that anaerobic metabolism contributed significantly to energy requirements, or that ischaemia was responsible for poor contractile function.

The study of myocardial free fatty acid metabolism is complicated by the activation of lipoprotein lipase by heparin.[28] We believe that adequate anticoagulation is mandatory for left heart catheterisation, and all patients in this study received heparin. In a previous study we showed that intravenous heparin administered one hour before catheterisation effectively attenuates the rise in arterial free fatty acids after a subsequent dose of heparin, and that within 30 minutes of this second dose, given at the time of arterial catheterisation, arterial concentration returns to control levels.[8] This regimen of two doses was used in this study.

Experiments with labelled palmitate have shown that in the normal heart there is myocardial lipolysis with release of free fatty acids into coronary venous blood.[29] Free fatty acids extracted by the heart may be esterified rather than oxidised immediately,[30] and free fatty acids derived from lipolysis may be oxidised.[30] Thus, measured extraction may not reflect true uptake, and true uptake, if it were known, does not measure the rate of oxidation. In addition, when the arteriovenous concentration difference is narrow, small errors in measuring concentrations will have a large effect upon estimated extraction. For these reasons the finding of significantly greater free fatty acid extraction and extraction ratio in the cardiomyopathy compared with the control group should be viewed with caution.

Despite these difficulties it is of great interest that release of neither free fatty acids nor glycerol was observed in the patients with cardiomyopathy, whereas free fatty acid release was found in two, and glycerol release in six of the nine control subjects. Release of free fatty acids and glycerol are also common in patients with coronary artery disease[8 31] and hypertrophic obstructive cardiomyopathy.[27] It cannot be concluded from this study that free fatty acid metabolism is abnormal in congestive cardiomyopathy, but this problem merits further investigation with labelled free fatty acids.

Because patients with congestive cardiomyopathy improve clinically during long-term administration of beta-blocking drugs[32 33] and relapse when they are withdrawn,[34] catecholamine excess or sympathetic overactivity have been suggested as pathogenic mechanisms.[33 34] Acutely catecholamines increase myocardial lipolysis[35] and the arterial concentration and myocardial oxidation of free fatty acids,[36] and inhibit pyruvate dehydrogenase.[37] The relatively low arterial free fatty acid concentrations, the absence of glycerol release, and the consistently high lactate extraction ratios in our patients do not suggest catecholamine excess. It is unlikely that the beneficial effect of beta-blocking drugs is the result either of changes in myocardial substrate extraction or relief of ischaemia.

In the control group the haemodynamic changes during pacing were normal,[38 39] whereas in the five patients with cardiomyopathy who were paced, end-diastolic pressure tended to rise and indices of contractility did not increase significantly. Coronary sinus blood flow increased substantially with heart rate in each control subject, but in only one patient with cardiomyopathy. Failure to increase flow with heart rate implies that the coronary vasculature is near maximal dilatation at rest. Under these circumstances coronary flow is critically dependent upon cardiac output and the length of diastole; in both of the patients who sustained reductions of coronary flow cardiac output decreased on pacing. Failure to augment coronary flow as heart rate increases in patients with severe aortic stenosis[40] or hypertrophic obstructive cardiomyopathy[27] is associated with myocardial lactate production. Lactate extraction remained high in each of our five patients. Thus, the myopathic heart does not resort to anaerobic metabolism even during the stress of pacing.

This study shows that the overall efficiency of the heart is severely reduced in congestive cardiomyopathy. Though there were small differences in substrate extraction between the two groups, no gross abnormality of oxidative metabolism was found in patients with congestive cardiomyopathy, suggesting that low efficiency lies in poor mechanical function rather than in deficient energy supply.

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Role of sympathetic nervous system in non-ischaemic ventricular arrhythmias

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SUMMARY Propranolol and nadolol were used in two groups of patients having ventricular arrhythmias. The two groups were characterised by differences in sympathetic drive. The 10 non-adrenergic patients had idiopathic, monomorphic extrasystoles (isolated with fixed coupling or in pairs or salvoes) arising from the right ventricle or the septum. These extrasystoles were chronic and benign, with a slightly increased daytime frequency (day:night = 1·6). They disappeared on exercise. The nine adrenergic patients had less frequent but more complex polymorphic ventricular extrasystoles, and rapid and irregular tachycardias which were resistant. They occurred predominantly during the day and were associated particularly with stress and exercise. They were either idiopathic, or coexisted with mitral valve prolapse (three cases) or hypertrophic subaortic stenosis (one case) in young patients (mean age, 32 years) who did not have coronary heart disease. Nadolol was more effective than propranolol in controlling the arrhythmia, heart rate, and variations in sinus rhythm in the adrenergic group, while the arrhythmia was not controlled in the non-adrenergic group. Using clinical variables, comparison of the frequency of extrasystoles by day and night, and assessment of the antiarrhythmic effect of beta-blockers, the role of the sympathetic tone in non-ischaemic ventricular arrhythmias may be elucidated.

The role of the sympathetic nervous system in ventricular arrhythmias has been shown experimentally[1-3] and suggested by clinical observations.[4-6] It has been difficult to determine which clinical variables most effectively demonstrate the significance of its influence, and hence the value of treatment by beta-blockade. This study uses clinical, electrocardiographic, and therapeutic indices to evaluate the role of sympathetic drive in 19 patients with ventricular arrhythmias of non-ischaemic origin.

Subjects and methods

GROUPS OF PATIENTS (Table)

The 19 patients in this study had ventricular arrhythmias in the absence of coronary heart disease or previous myocardial infarction, and there was no cardiac, respiratory, or gastrointestinal contraindication to beta-blockade. They were allocated to one of the two groups on the basis of their tolerance of the arrhythmia and the precipitating factors. Patients who could indulge in simple activities without palpitation were assumed to be insensitive to catecholamines and allocated to the non-adrenergic group. Patients complaining of palpitation that occurred exclusively in association with effort or that was aggravated by emotion were classified as adrenergic.

The non-adrenergic group comprised six male and four female patients, with a mean age of 41 (range = 10 to 67). The arrhythmia was discovered either at routine examination (cases 1 to 6) or as a result of investigating "skipping of heart beat" at rest. Cardiovascular examination included electrocardiogram and echocardiogram, clinical, and radiological examination. The normal physical activity of these patients was undisturbed by their idiopathic ventricular extrasystoles. The four male and five female patients of the adrenergic group had a mean age of 32 (range = 12 to 55), and suffered far more striking arrhythmias. Cases 11 to 13 were children with syncope of effort resulting from rapid and irregular ventricular tachycardia. They have been reported.[7] Two young women (cases 14 and 15) had similar histories, but

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Table *Clinical, electrocardiographic, 24 hour monitoring, and exercise data for non-adrenergic (cases 1 to 10) and adrenergic (cases 11 to 19) patients during control period and on beta-blocking therapy*

Case No.	*Sex*	*Age*	*A. Orig.*	*Control*			*Propranolol*			*Nadolol*			*Exercise*		
				CF	Δ	*ES/h*	*CF*	Δ	*ES/h*	*CF*	Δ	*ES/h*	*C*	*P*	*N*
Non-adrenergic group															
1	F	35	LV ant	88·4	88	130	81·9	68	231	76·3	45	309	ES=	ES=	ES=
2	M	60	LV sept	77·5	47	89	62·8	32	13	55·8	25	12	ES−	0	0
3	M	67	RV	65·1	57	307	62·6	50	198	58·9	55	499	ES−		
4	M	50	LV sept	76·9	78	32	65·9	54	5	62·7	24	32	ES=	ES=	0
5	M	53	RV sept	72·6	42	1240	60·4	36	534	52·7	33	425	0	0	0
6	F	48	RV sept	67·2	48	577	82·4	80	792	76·4	57	178	0	0	0
7	M	43	RV sept	89·8	78	1105	71·9	50	908	62·5	33	809	0	0	0
8	M	18	RV apex	71·9	46	247	82·6	78	363	67·6	58	503	0	—	0
9	F	10	LV apex	69·6	91	358	62·2	78	57	56·4	53	0	0	0	0
10	F	30	RV sept	67·9	60	690	55·7	44	489	50·0	47	597	0		
Adrenergic group															
11	M	12	LV mult	69·8	91	99	60·1	66	49	56·0	49	24	VT	ES+	0
12	F	13	LV mult	62·7	71	121	56·1	68	51	56·8	47	21	VT	VT	ES
13	F	17	LV mult	89·2	84	69	65·4	47	7	56·0	42	1	VT	ES	0
14	F	29	LV mult	84·2	68	913	66·0	60	507	68·3	42	291	VT	ES	0
15	F	39	LV—RV	72·4	74	110	57·8	43	56	55·6	45	33	ES+	0	0
16	F	55	LV—RV	83·3	70	159	69·5	46	72	55·2	27	88	ES	0	0
17	M	59	LV mult	71·8	66	122	62·9	40	73	64·6	33	34	ES+	0	0
18	M	26	RV	88·7	93	111	69·3	54	81	70·3	46	78	ES+	VT	ES
19	M	36	LV	84·0	70	102	66·3	63	104	60·7	30	52	—	VT	ES

Abbreviations: A. Orig., arrhythmia origin; C, control; CF, cardiac frequency/minute; Δ, range of sinus frequency in the 24 hour period; ES/h, hourly extrasystolic rate over the 24 hour period; ES=, unchanged extrasystolic rate at exercise; ES−, decreased extrasystolic rate at exercise; ES+, increased extrasystolic rate at exercise; N, nadolol; P, propranolol; LV, left ventricle; RV, right ventricle; ant., anterior wall (of the LV); mult, multiform; sept, septum.

(*Note:* cases 8 and 15 received acebutolol instead of propranolol.)

their symptoms were less severe and had evolved over a long period. Palpitation without dizziness was a feature of cases 16 and 17. Finally there were two patients (cases 18 and 19) in whom exercise or emotional stress precipitated sustained paroxysmal ventricular tachycardia which was not self-limiting.

The adrenergic group underwent thorough investigation. All cases were subjected to cardiac catheterisation with left ventricular angiography. No risk factors were identified in this or the other group and there was no clinical or electrocardiographic evidence of coronary artery disease. Cases 18 and 19 underwent additional coronary angiography to exclude congenital abnormalities of the coronary arteries. Case 19 had undergone surgery four years previously for hypertrophic cardiomyopathy. Three cases of mitral valve prolapse were discovered (cases 14, 16, and 17). Urinary catecholamines were normal in this group, as were serum catecholamines in cases 11 to 13, while the latter were at the upper limit of normal in case 19.

ELECTROCARDIOGRAPHIC ANALYSIS

Standard 12 lead electrocardiograms were obtained and the morphology of the ventricular arrhythmias was thereby demonstrated. Exercise tests were performed with electrocardiographic monitoring. Work increments of 20 to 30 W of one minute duration were used. The end-point in the non-adrenergic group was taken to be disappearance of the arrhythmia, while in the adrenergic group it was the onset of arrhythmia and symptoms. The same exercise test was repeated when the patient was on beta-blocking therapy.

Endocavitary studies were not routinely performed. In the non-adrenergic group, six cases were explored (cases 1, 3, 5, 6, 9, 10). The remainder were not studied as their arrhythmias were considered too benign to justify invasive exploration and 24 hour monitoring yielded sufficient information. In the adrenergic group, all but one patient (case 15) were explored. Case 15 had an arrhythmia considered so severe that treatment was initiated. In all cases the arrhythmias were studied with atrial stimulation and with small doses of isoprenaline. In cases 9, 10, 18, and 19, attempts were made to intitiate sustained ventricular tachycardia by right ventricular stimulation, but they failed.

AMBULATORY ELECTROCARDIOGRAPHIC MONITORING

The number of ambulatory recordings (using Avionics and Dynagram recorders) depended on clinical need and changes of medication. Previous electrocardiograms or 24 hour recordings were available for most patients while undergoing treatment other than that given during this study. They confirmed the stability of the arrhythmias. Patients in the non-adrenergic group were monitored for a mean of 6·8 days (range four to 13). Patients in the adrenergic group, with uncommon and more resistant arrhythmias, underwent monitoring for a mean of 12·3 days (range six to 22). A total of 179 24 hour recordings was obtained: 49 control tracings (mean

2·6, range one to six), 88 with nadolol (mean 4·6, range one to 19), and 42 with another beta-blocker (mean 2·2, range one to four).

The ambulatory recordings were analysed by the ATREC computer program.[8] In addition to analysis of the 24 hour period, two periods, from 10.00 hours to 18.00 hours and 01.00 hour to 05.00 hours were analysed separately. The hourly rate for the following categories of extrasystole was computed: isolated ventricular extrasystoles, pairs, and salvoes. For salvoes, only the first 10 beats were taken to be ventricular extrasystoles, if followed by ventricular tachycardia. To simplify the results, the overall number of ventricular extrasystoles is reported. There were four cases with several control tracings of which those with runs of sustained ventricular tachycardia (in cases 18 and 19) or long salvoes (in cases 9 and 10) were eliminated. This was done as it was impossible to quantify the ventricular extrasystoles in these severe arrhythmias in a logical manner comparable to that for less severe arrhythmias. This bias did not lead to unmerited conclusions concerning the efficacy of treatment. It also gave a clearer quantitative breakdown for comparison with recordings while under treatment.

The mean heart rate was evaluated at 10 minute and hourly intervals. The overall cardiac rate was considered to be of sinus origin when the ventricular extrasystoles were isolated and followed by a compensatory pause. Frequent coupled beats, salvoes, sustained or frequent ventricular tachycardia result in apparently raised rates, but in these instances the ventricular rate does not reflect the sinus rate. In computing the minimum and maximum rates, by measurement of the fastest and slowest rates of a sliding 16 beat RR interval, these errors were eliminated by careful selection of the tracings used. The gradient "delta" of the sinus rate is determined by the difference between minimum and maximum rates over the 24 hour period and reflects the spontaneous variability of the sinus rate of ambulatory patients.

TREATMENT WITH BETA-BLOCKERS

Each patient underwent treatment with two beta-blockers, the order of which was randomised. Dosage of the drug was determined by weight and severity of the rhythm disturbance. In 17 patients, propranolol was used as the baseline medication, while acebutolol was used for two patients. Acebutolol, 200 mg, was taken to be equivalent to 40 mg of propranolol. The q.i.d. dose of propranolol was 120 ± 23 mg/day for the non-adrenergic group and 142 ± 60 mg/day for the adrenergic group. Nadolol was administered once daily in the same dose as for propranolol. The minimum duration of treatment was four days for each drug, with a mean of seven days for propranolol and 12 days for nadolol. The difference is accounted for by the long-term use of nadolol in some adrenergic patients. Evaluation of each drug was performed after comparable durations of treatment.

Statistical evaluation was done on the raw data for the mean cardiac rate and the delta sinus rate, and after logarithmic transformation for the rate of ventricular extrasystoles. The Mann-Whitney test was used to compare the two groups and analysis of variance performed to compare the two therapeutic trials with the controls. Qualitative differences were checked by the exact test. Data are expressed as mean ± standard deviation in the text, but by mean ± standard error in the Figures.

Results

Indices including electrocardiograms, exercise tests, and ambulatory recordings were studied for the control and subsequent treatment periods. The two groups could not be differentiated on the basis of age ($p = 0{\cdot}25$), sex ($p = 0{\cdot}29$), or drug dosage ($p = 0{\cdot}80$).

BASELINE CHARACTERISTICS OF VENTRICULAR ARRHYTHMIAS

(1) Origin and distribution of the arrhythmias (Table)
The QRS morphology is clearly different in the two groups of patients. In the non-adrenergic group, the origin of the ventricular extrasystoles is the right ventricle in six patients (one apical, four septal) and the left ventricle in four patients (two septal). All the complexes of ventricular origin are monomorphic (Fig. 1) except in case 3, where the first of the coupled beats was of right ventricular origin, while the second was either identical or arose elsewhere in the right ventricle.

In the adrenergic group, the origin was exclusively the left ventricle in six patients (cases 11, 12, 13, 14, 17, 19), the right ventricle in one (case 18), and both right and left ventricle in two (cases 15 and 16) (Fig. 2). There were significant differences between the groups in terms of the ventricular origin of arrhythmias ($p<0{\cdot}04$) and in terms of the uniformity of the ventricular complexes ($p<0{\cdot}001$).

The coupling interval and the grouping of the arrhythmias also differentiate the two groups. In the non-adrenergic one, the coupling interval varied within a narrow range of 400 to 600 ms, with the exception of case 1 which demonstrated true parasystole. The ventricular extrasystoles were isolated in cases 1, 4, 5, and 6; pairs were present in cases 2, 3, 7, and 8, and there was frequent sustained ventricular tachycardia or repetitive long salvoes, almost regular at a rate of 150 to 200 per minute in cases 9 and 10.

In the adrenergic group, a greatly changing coupling interval was the rule, with frequent R upon T phenomena. All patients had doublets and ventricular

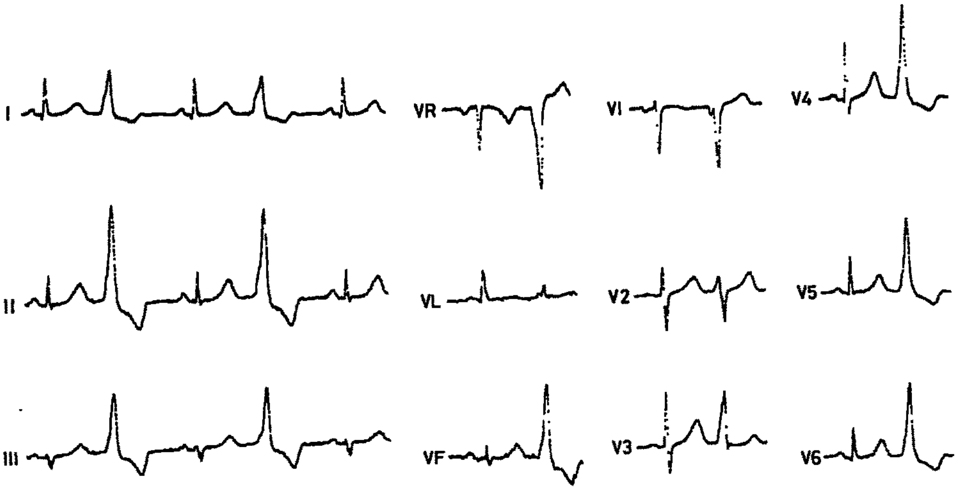

Fig. 1 *Typical 12 lead electrocardiogram in the non-adrenergic group (case 6). QRS complexes of ventricular origin have a long and constant coupling interval, with frequent bigeminy. Note the vertical axis and the left bundle-branch block pattern, suggesting a high septal origin.*

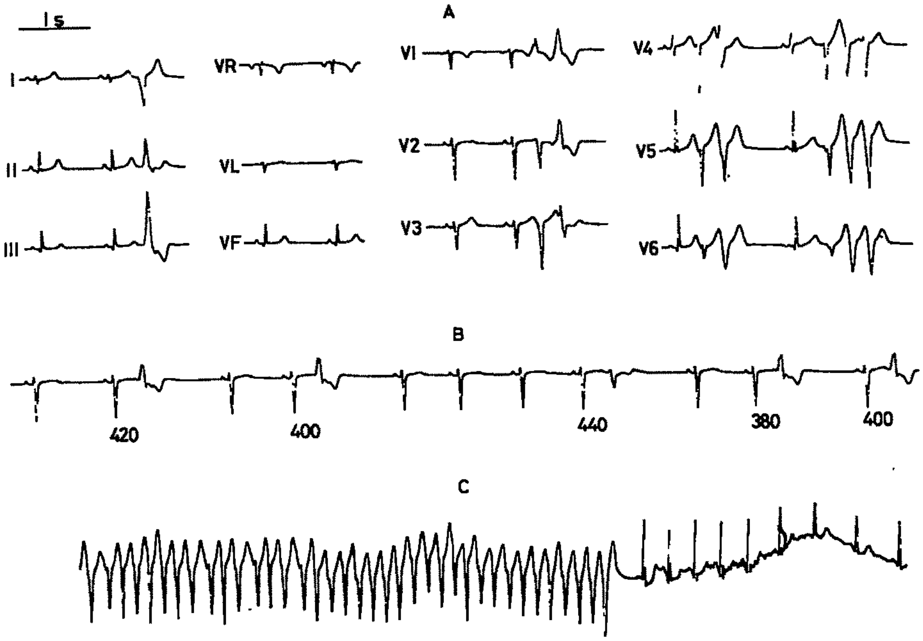

Fig. 2 *Typical electrocardiogram in the adrenergic group (case 14). Ventricular extrasystoles are polymorphic, of left ventricular origin, and grouped in pairs or short salvoes (A). The coupling interval is variable (B). It is often short with R upon T phenomena. Runs of very rapid and irregular ventricular tachycardia are observed on exercise (C).*

tachycardia, the latter being monomorphic only in case 18. The ventricular tachycardia was of short duration (10 to 15 beats) in cases 16 and 17, more sustained and irregular in cases 15 and 19, and particularly rapid (up to 300/minute), irregular, and polymorphic in cases 11 to 14. The two groups showed a difference in the incidence of isolated ventricular extrasystoles and doublets as compared with salvoes and sustained ventricular tachycardia ($p<0{\cdot}001$).

(2) *Endocavitary electrophysiological tests*

Exploration was carried out in 14 patients and showed clearly different phenomena in the two groups, but did not establish the mechanisms of the arrhythmias. In four patients (cases 9, 10, 18, and 19), attempts at initiating or terminating ventricular tachycardia by pairs or repetitive stimuli did not give reliably reproducible results. The behaviour of the ventricular extrasystoles as a function of the atrial stimulation rate was variable. In the non-adrenergic group, five patients (cases 3, 5, 6, 9, 10) had extrasystoles which were dependent on the atrial rate through a range of frequencies with minimum and maximum threshold values. This was not true of case 1 with parasystole. Bi-, tri-, and quadrigeminy were seen to appear and disappear in relation to the atrial rate and occurred mostly with fixed coupling. These characteristics were disclosed on ambulatory monitoring in the remaining patients who were not explored. In the adrenergic group, the incidence of ventricular extrasystoles was hardly influenced by the atrial stimulation rate. They disappeared only by overdriving the ventricles and their frequency only increased on exercise testing, but not with acceleration of the pacing rate. The administration of small doses of isoprenaline gave results comparable with those obtained on exercise testing. In the non-adrenergic group, it reduced the number of ventricular extrasystoles precipitated by acceleration of the sinus rate. In cases 9 and 10, however, it increased the duration and the rate of the salvoes while reducing their incidence. Of the patients in the adrenergic group who were explored and given isoprenaline, their ventricular arrhythmias were aggravated, with salvoes which were longer, faster, and poorly tolerated.

(3) *Exercise testing* (Table)

In six cases of the non-adrenergic group, the ventricular extrasystoles disappeared with effort on reaching a threshold value of the sinus rate (Fig. 3). In only two cases did the rate of ventricular extrasystoles diminish without complete disappearance. In a further two cases, the relative rate of ventricular extrasystoles was not modified by the sinus rate; hence there was an increase in the absolute number of ventricular extrasystoles per minute with the increase in the sinus rate.

All patients in the adrenergic group underwent

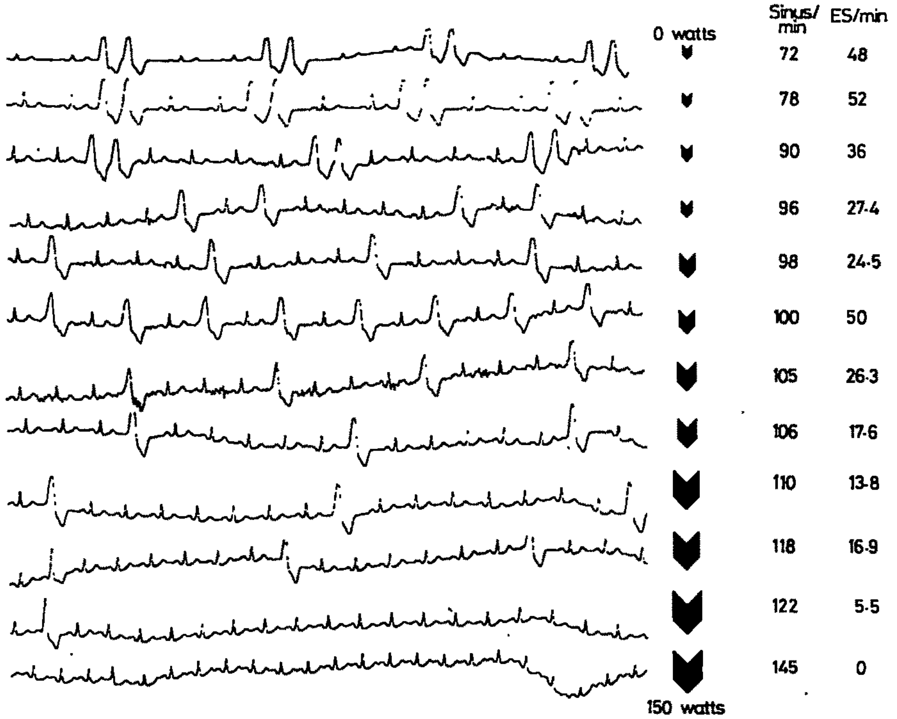

Fig. 3 *Typical exercise profile of a non-adrenergic patient. As effort was progressively increased from 0 to 150 watts, the sinus rate increased from 72 to 145 beats/minute. The number of ventricular extrasystoles (ES) is closely related to the sinus rate, viz. pairs, isolated ventricular extrasystoles, bigeminy, trigeminy, etc. The net result is either an increase or decrease in the absolute or relative ventricular extrasystolic rate. The general tendency, however, is a progressive disappearance of the ventricular arrhythmia.*

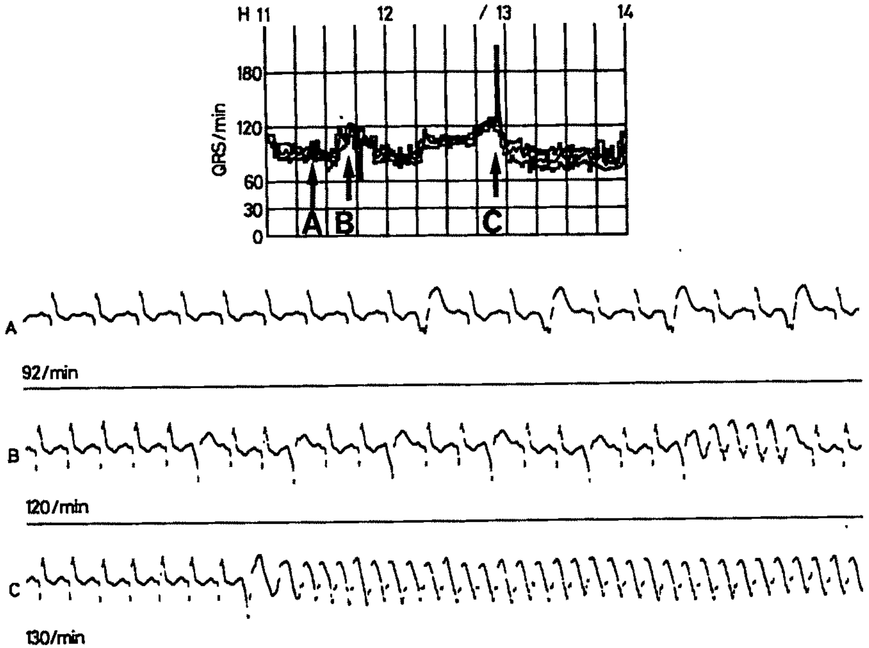

Fig. 4 *Parallelism of sinus rate and ventricular arrhythmia in an adrenergic patient (case 19). Above is the computerised analysis of a three-hour continuous tracing expressed in terms of minimum, mean, and maximum frequency curves. The tracings corresponding to periods A, B, C are shown below. During A, the sinus rate is 92/minute and trigeminy is noted. During B, there is a rate of 120/minute, the coupling interval of isolated ventricular extrasystoles is shortened, and a run of five beats of different morphology is seen. During C, the rate is 130/minute, and ventricular tachycardia at a rate of 230/minute occurs.*

exercise testing with the exception of case 19 in whom exercise induced a poorly tolerated ventricular tachycardia (Fig. 4). In the remaining eight, exercise induced ventricular tachycardia in four, caused an increased frequency of short runs of ventricular tachycardia in three, and caused an absolute and relative increase in the frequency of ventricular extrasystoles in one.

(4) Ambulatory electrocardiographic monitoring (Table, Fig. 5)
In the non-adrenergic group, the hourly rate of ventricular extrasystoles was 478 ± 439. The difference between daytime (591 ± 462) and night time (361 ± 514) rates was not significant ($p>0{\cdot}1$) with a ratio of 1·6. The mean cardiac rate over 24 hours was 74·7 ± 8·6/min and was greater during the day (82·9 ± 9·6) than at night (65·8 ± 9·6) ($p<0{\cdot}01$), the ratio being 1·26. Delta over 24 hours was 64 ± 20/min, the average maximum rate was 121/min, and the average minimum rate was 57/min.

In the adrenergic group the hourly rate of ventricular extrasystoles was 201 ± 267. The difference between the daytime rate (252 ± 390) and the night time (84 ± 78) was significant ($p<0{\cdot}05$), with a ratio of 3. The cardiac rate over 24 hours was 78·5 ± 9·3 and was greater by day (87·0 ± 10·5) than by night (64·4 ± 8·4) ($p<0{\cdot}01$) with a ratio of 1·35. Delta over 24 hours was 76 ± 10 with an average maximum of 130/min and average minimum of 54/min.

There were significant differences between the two groups for the day:night ratios of rates of ventricular extrasystoles, 1·6 to 3 ($p<0{\cdot}05$) and heart rates, 1·26 to 1·35 ($p<0{\cdot}05$). There was a difference in the delta values ($p<0{\cdot}05$).

EFFECTS OF TREATMENT WITH BETA-BLOCKERS (Table, Fig. 6 and 7).

(1) Effects of propranolol

In the non-adrenergic group, propranolol (and acebutolol when it was used) does not modify the incidence of ventricular extrasystoles found on exercise testing ($p=0{\cdot}37$) (Table). There is a decrease of 23% in the rate of ventricular extrasystoles in 24 hours, but this was not found to be statistically significant. Neither the average heart rate in 24 hours (−8%) nor the delta value (−11%) was significantly altered (Fig. 7).

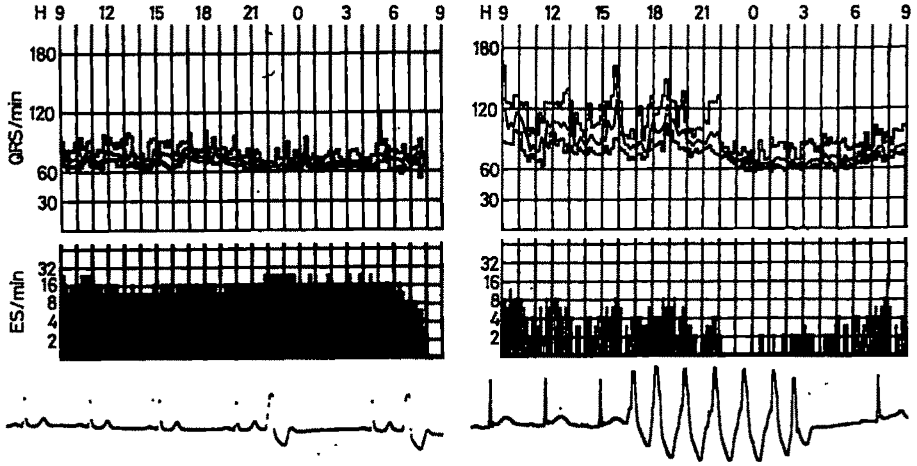

Fig. 5 *Typical continuous 24 hour electrocardiogram for the non-adrenergic group (case 5) and for the adrenergic group (case 18). Left, the ventricular extrasystolic rate remains constant all day and the heart rate does not vary greatly between day and night. The minimum and maximum frequency curves closely approximate the mean heart rate, the difference, delta, being 40/minute. Right, the ventricular extrasystolic rate varies with the mean heart rate. Delta is greater, 70/minute.*

In the adrenergic group, exercise testing during treatment with propranolol resulted in ventricular tachycardia in two cases as compared with four during the control period. Case 19, who did not undergo this test, was found to have persistent ventricular tachycardia, but at a reduced rate. Numerous ventricular extrasystoles were seen in three cases, yet none could be induced by exercise in a further three. There was an overall reduction in the number of ventricular extrasystoles in 24 hours of 46% ($p<0{\cdot}01$). It is important to note that the reduction is significant only for the daytime incidence (Fig. 6). The cardiac rate fell by 19% over 24 hours ($p<0{\cdot}01$) and delta by 29% ($p<0{\cdot}01$).

(2) Effects of nadolol

In the non-adrenergic group, exercise testing resulted in the almost complete disappearance of the ventricular extrasystoles. The number of extrasystoles over 24 hours was not modified (−6%) and there was no difference between daytime and night time incidence. The cardiac rate over 24 hours was reduced by 17% ($p<0{\cdot}01$) and the delta by 32% ($p<0{\cdot}01$).

In the adrenergic group, there was no case of exercise-induced ventricular tachycardia, while ventricular extrasystoles were noted in only three patients. The number of ventricular extrasystoles over 24 hours was diminished by 66% ($p<0{\cdot}01$) and was lower both by day and by night. The mean cardiac rate was reduced by 17% ($p<0{\cdot}01$) and delta by 34% ($p<0{\cdot}01$).

Discussion

From experimental and clinical observations, there is no doubt of the influence of sympathetic tone on ventricular arrhythmias, particularly in the presence of myocardial ischaemia.[9–11] It remains difficult to establish, in individual cases, whether a particular arrhythmia is dependent on sympathetic drive. It seems that sympathetic tone plays either a major or a contributory role in the generation of arrhythmias. This is certainly true of ischaemic arrhythmias which depend on the vago-sympathetic balance, but has also been observed in denervated hearts.[12] We therefore elected to eliminate patients with coronary artery disease from this study. The heart was normal in all respects, except for the arrhythmia, both at rest and on exercise in the 10 non-adrenergic patients. Coronary artery disease in the adrenergic group was excluded on the basis of the following: age (mean = 32 years), absence of history, symptoms, suggestive abnormalities on the electrocardiogram (both at rest and on exercise), left ventricular angiography and, in two cases, coronary angiography.

We deliberately selected patients with palpitation occurring only at rest or only on exercise, this being apparent from the history. It appears that this preliminary and simple qualitative selection screen correlates well with the more sophisticated and quantifiable tests subsequently performed. These included electrocardiogram, exercise tests, electrophysiology, 24 hour monitoring, and therapeutic findings. While

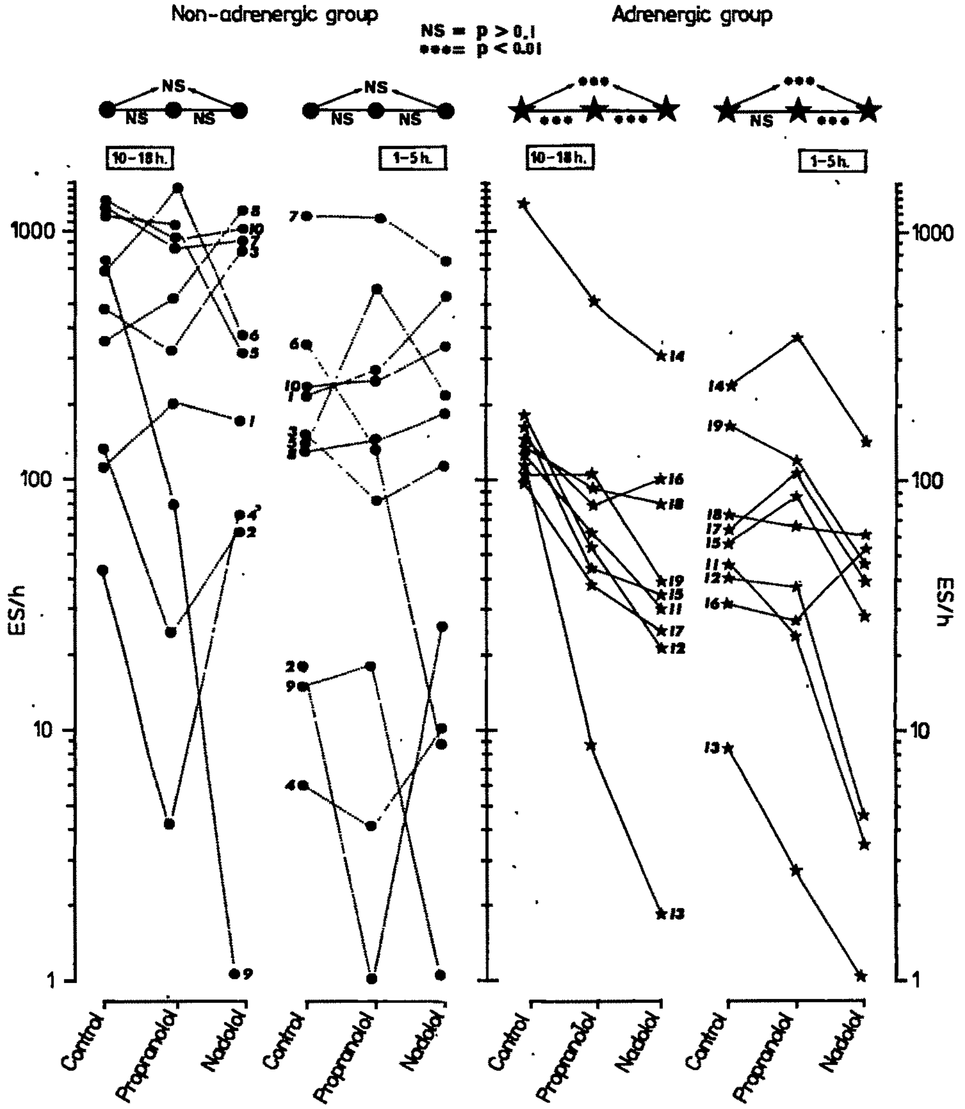

Fig. 6 *Comparison of the hourly ventricular extrasystolic rate between the non-adrenergic group and the adrenergic, for both day and night and during control and therapeutic periods. Left, the non-adrenergic patients (solid circles). The left-hand column represents daytime, from 10 am to 6 pm, and the right, night time, from 1 am to 5 am. There is no significant difference between the groups. Right, the adrenergic patients (solid stars). Left-hand column again shows daytime results, conversely the right-hand column. The daytime ventricular extrasystolic rate is significantly lowered by beta-blockade, especially by nadolol. At night, the effect is not significant with propranolol, but is significant with nadolol.*

some indices were applicable to either group as a whole, there were discrepancies when applied to certain individual cases. For example, cases 9 and 10 of the non-adrenergic group shared characteristics with patients of the adrenergic group. The converse was true of cases 18 and 19 of the adrenergic group. None the less, two contrasting patterns of ventricular arrhythmia emerge from the cases studied. Thus assessment of the mechanism of the arrhythmias is facilitated and therapeutic consequences are disclosed.

NON-ADRENERGIC VENTRICULAR ARRHYTHMIAS

The non-adrenergic patients were found to have

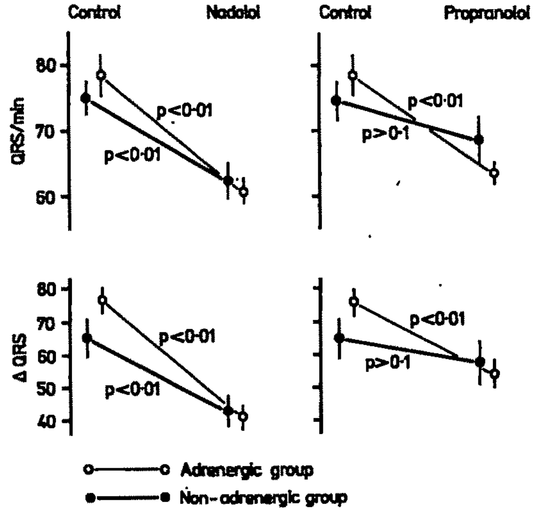

Fig. 7 *Mean cardiac rate and delta values during control and treated periods. The mean cardiac rate over 24 hours is shown above. The control values (mean + SE) are not different for the two groups and both are significantly reduced by nadolol. Propranolol causes a significant reduction in the adrenergic patients only. Delta values are shown below and the same trends are seen. In addition, this index is significantly different for the two groups during the control period ($p<0\cdot05$).*

chronic and benign arrhythmias which were, in general, detected at routine examination. Some of these patients complained of a sensation of the heart skipping beats, occurring at rest and disappearing on exercise. There was no organic heart disease in this group. The ventricular extrasystoles were mostly monomorphic, being of right ventricular or septal origin, with a relatively long coupling interval which varied within narrow limits (400 to 600 ms). Bi-, tri-, and quadrigeminy was frequently observed and the occurrence of arrhythmias was dependent on the sinus rate[13 14] between two thresholds. Usually the lower one was apparent at rest, or at night, from 24 hour electrocardiograms. More important is to determine the upper one by accelerated atrial pacing or exertion. It was the arrhythmia observed during, and not after, exercise which was subject to evaluation. A range of arrhythmias was seen, from paired beats, which were not unusual, to sustained ventricular tachycardia. Salvoes three or 10 beats long, or even 20, were quite frequent, with rates of 150 to 200/min. When paired beats or short salvoes were seen, their rate and duration sometimes increased initially with effort before subsequently disappearing, as did the isolated ventricular extrasystoles.

ADRENERGIC VENTRICULAR ARRHYTHMIAS

These arrhythmias present a clear contrast to the preceding group. They are far less common, the nine cases being drawn from a five year period during which patients were referred to our department specifically for management of severe arrhythmias refractory to treatment. Had the "control" group of non-adrenergic patients been collected over the same period, there would be in excess of 10 or 20 times the number in the group. The adrenergic arrhythmias were, in all cases, symptomatic and in certain instances, life-threatening.

Organic heart disease was established in four patients. The three cases of mitral valve prolapse supported the hypothesis of an associated hyperadrenergic state.[15] Purely catecholamine-dependent arrhythmias, with no detectable heart disease, were clearly seen in three children in this group.[7] Raised levels of urinary catecholamines were not, however, found in the adrenergic group; thus the arrhythmias appear to be related to catecholamine sensitivity rather than to a hyperadrenergic state.

The arrhythmias were polymorphic, of left ventricular origin, and with a variable but often short coupling interval. There were short, rapid, and irregular salvoes, the rate of which often exceeded 200/min. Exercise tests were limited by the symptoms induced in every case. Significant electrocardiographic abnormalities were noted before the patients, accustomed to their arrhythmias, started to complain of symptoms. Atrial pacing did not influence the arrhythmias, in contrast to both infusion of isoprenaline and exertion. The sensitivity to the isoprenaline, but not the dosage, differentiates the two groups studied.

AMBULATORY MONITORING

Ambulatory recordings showed that the rate of ventricular extrasystoles for the non-adrenergic group was higher than for the adrenergic one ($p<0\cdot05$). The Table and Fig. 6, however, indicate that this criterion cannot be used to differentiate the individuals from either group. The rate of ventricular extrasystoles varied within wide limits and was a function of activity. It decreased with activity in the non-adrenergic patients and increased with the others. The day:night ratio for the rate was found to be a more reliable expression of the same concept, again showing a significant difference between the two groups ($p<0\cdot05$). Subjects could not be differentiated on this basis either. It can be seen from Fig. 6 that only one adrenergic patient exceeds a nocturnal ventricular extrasystolic rate of 100/hour, while six patients of the non-adrenergic group exceeded this rate. Because of a lower threshold sinus rate for arrhythmias, the remaining four non-adrenergic patients were found to have a low rate of ventricular extrasystoles during sleep.[16] The mean cardiac rate was not significantly different in the two groups, though higher in the adrenergic group. The day:night ratio (1·26:1·35, non-adrenergic:adrenergic) and the delta values were, on the other hand, significantly different ($p<0·05$). The latter values express the maximum amplitude of the variation in sinus rate and are very sensitive, reflecting the pattern given by the computer analysis (Fig. 5).

THERAPEUTIC EFFECT OF BETA-BLOCKADE

Two drugs were used, of which propranolol served as a reference and nadolol as the more powerful agent. This represents a further approach to the problem of the mechanism of arrhythmias. The role of other drugs as membrane stabilisers is not discussed in this article. The two groups respond in opposite ways to quinidine and quinidine-like agents, however, the non-adrenergic patients being sensitive and the adrenergic patients being resistant. The converse was true for beta-blockers.

The arrhythmias were not suppressed in the non-adrenergic group by propranolol or nadolol, though they may have been influenced. Fig. 6 clearly shows that the rate of ventricular extrasystoles may rise, fall, or remain the same with either drug by day or by night. These changes were mainly related to the sinus rate, the arrhythmias featuring in the range of sinus rates between upper and lower threshold values. Thus the arrhythmias may have been more or less manifest on this basis. In the adrenergic group, however, there was always improvement with beta-blockade. Complete control of the arrhythmias was not necessarily achieved though the arrhythmias were heavily dependent on sympathetic drive, and some patients improved further on addition of quinidine. Detailed examination of the results showed that in the non-adrenergic group, the rate was unchanged by nadolol (−6%) but diminished by 23% by propranolol. This is not statistically significant, but raises the question of the quinidine-like effect of propranolol which has been proven experimentally yet is not supported by clinical evidence.

In the adrenergic group, nadolol is effective by day and night, whereas propranolol was effective only by day. This suggests that the dependence of the arrhythmias on the sympathetic drive is more obvious by day, so that the less powerful agent (propranolol) has a more visible effect during the day. Propranolol and nadolol have different effects on the cardiac rate and the delta value. These are unaffected by propranolol in the non-adrenergic group, but quite significantly altered in the adrenergic group. Nadolol, on the other hand, modifies these indices in both groups, though to a greater extent in the adrenergic group. While there is a difference in the control values for delta between the two groups, no such difference exists for cardiac rate or delta while nadolol was administered.

These quantifiable results correlate with the symptomatic improvement described by the patients, which was greater with nadolol than with propranolol. Currently, six patients (cases 11 to 13, 15, 18, 19) are controlled on long term nadolol therapy, having been incompletely controlled by propranolol alone. It may be argued that propranolol appears less effective, but that this is attributable to using the same doses for both nadolol and propranolol. If, however, the dose of the latter is doubled, only modest therapeutic gain is achieved. No such gain was noted when the dose of nadolol was doubled.

In conclusion, there appears to be correlation between ventricular extrasystoles, cardiac rate, and the maximum variations in sinus rate on the one hand, and clinical symptoms and electrocardiographic findings both at rest and on exercise.[17] The behaviour of the arrhythmias observed under the influence of beta-blockade confirms that there is an important contribution from the sympathetic nervous system in certain ventricular arrhythmias. Conversely, the absence of antiarrhythmic effect noted in other cases treated with beta-blockers sheds light on the mechanism of these. It is also of value in establishing the indication for using various drugs. The cases intermediate between the extremes of the range studied may represent a mixed picture where an arrhythmia is influenced by, but is not completely dependent on, sympathetic drive, providing an indication for combined therapies.

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New prognostic criteria for children with cyanotic congenital heart disease

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SUMMARY Available oxygen and oxygen unloading capacity were determined at the time of cardiac catheterisation, from blood gas analysis, p 50 in vivo, and haemoglobin, in 79 children with cyanotic congenital heart disease, their age ranging from 2 weeks to 14 years. The patients were followed up for six months to find out how many of those without surgical intervention survived. Actuarial analysis showed that the six month survival rate among the patients with low available oxygen or oxygen unloading capacity was significantly lower (24% and 49%, respectively) compared with those with normal indices (90% and 96%, respectively). Both available oxygen and oxygen unloading capacity were superior to arterial oxygen saturation and arterial oxygen content as prognostic criteria. Haemoglobin and haematocrit were of little value in prognosis. Available oxygen appeared to be the best prognostic criterion for survival at six months. It is concluded that available oxygen and oxygen unloading capacity are useful prognostic criteria in children with cyanotic congenital heart disease. These new criteria, when used in conjunction with the conventional methods of assessing the cardiac lesion, may be of considerable help to the physician in evaluating the prognosis of the patient.

Children with cyanotic congenital heart disease have considerable mortality, especially in infancy,[1] if not operated on. Recent advances in cardiac surgery[2 3] have made it possible to save many of these infants. In order to salvage more of them, the clinician must be able to select patients who would soon die if not operated on. This approach is particularly important if the institution has limited resources for the investigation and treatment of these patients, for example, when there is a long waiting list for surgery.

The feasibility of surgery for a particular patient is usually assessed after a complete examination, including cardiac catheterisation and angiography. Anatomical considerations are of paramount importance when assessing operability in cyanotic congenital heart disease. The assessment of the urgency of the need for surgery tends to be based also on anatomical data and the knowledge of the natural history of each anatomical subgroup. It would be useful if physiological prognostic criteria could be developed, especially if these criteria could be applied independently of detailed anatomical considerations.

In cyanotic congenital heart disease, hypoxaemia limits the amount of oxygen available to the tissues. From first principles, it appears likely that the prognosis of children with cyanotic congenital heart disease may be related to oxygen availability to the tissues. As obligatory tissue oxygen consumption in children with cyanotic congenital heart disease remains unchanged,[4] the resultant decrease in oxygen to the tissues necessitates some compensatory adjustment. In serious cyanotic congenital heart disease, the ability to increase the cardiac output is often limited, and compensation mediated through haematological means becomes more important, for example, increase in red cell mass, 2,3-diphosphoglycerate (2,3-DPG) levels and in the haemoglobin-oxygen affinity,[4–6] thereby helping to increase delivery of oxygen to the tissues. Two haematological indices have been developed recently to quantify oxygen availability to the tissues: oxygen unloading capacity[7] and available oxygen.[8]

The purpose of this study is to evaluate the usefulness of oxygen unloading capacity and available oxygen as prognostic criteria in children with cyanotic congenital heart disease.

Patients and methods

All children with cyanotic congenital heart disease

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catheterised in the University Department of Paediatrics, Singapore General Hospital (from December 1976 to April 1980), form the subjects for study, which was prospective. As a policy, all children with cyanotic congenital heart disease were submitted to cardiac catheterisation. Exceptions were because the parents did not consent or there was a shortage of catheter time, with the result that some children died before cardiac catheterisation. These children were excluded from the study.

In this study there were 79 children, whose ages ranged from 2 weeks to 14 years. Haemoglobin and haematocrit were determined on the day of cardiac catheterisation. At the time of cardiac catheterisation, venous blood, obtained from the right atrium, and arterial blood, obtained from the aorta or femoral artery, were sent for blood gas analysis. (Mixed venous blood is not necessary for the purpose of the calculations below, and peripheral venous blood can also be used.[9]) Haemoglobin was measured by the Corning Eel Hemoglobinometer using the cyanmethaemoglobin method, while haematocrit was estimated by Quick Fit Micro-haematocrit Centrifuge and Micro-capillary reader. Blood gases were analysed using the Corning model 165 pH/blood gas analyser. Oxygen saturation was directly estimated by American Optical Micro Reflection Oximeter.

p 50 standard, the partial pressure of oxygen when the haemoglobin is 50% saturated with oxygen under standard conditions (37°C and pH 7·4), was calculated using the pH, oxygen saturation, and oxygen tension of the venous blood.[9] p 50 in vivo was then calculated from the p 50 standard, correcting for pH and base excess measured on arterial blood.[10] The next mathematical manoeuvre involved the calculation of percentage saturation of haemoglobin at an arbitrary oxygen tension of 40 mmHg (Y 40) and at oxygen tension of 20 mmHg (Y 20), employing Hill's empirical equation,[11,12] with the use of p 50 in vivo for placement of the oxygen dissociation curve.

The oxygen unloading capacity was calculated[7] from the arterial oxygen saturation, Y 40, and haemoglobin. Available oxygen was similarly calculated,[8] using Y 20 instead of Y 40. At the time of study all patients had normal body temperature. The normal levels of available oxygen and oxygen unloading capacity were taken to be above 9·6 and 2·0 ml/dl, respectively.[13,14]

The patients were followed up for a period of six months after cardiac catheterisation to determine how many died during this period without operation. Indications for surgery were assessed using conventional criteria (since it would be unethical to withhold surgery from those who could be operated upon). The children submitted to operation were considered as "lost to follow-up", since the purpose of this project was to assess the natural history of children with cyanotic congenital heart disease in relation to oxygen unloading capacity and available oxygen. Life table analysis with maximum use of the data was carried out using the method described by Cutler and Ederer.[15] The difference between two means was assessed using Student's t test and the difference between two proportions was evaluated using the binomial distribution.

Results

Out of the 79 patients in this study, there were 49 children with "complete" follow up for six months (those who were not operated on and not lost to follow up): 30 remained alive at six months while 19 died during this period. Twenty-six children were operated on and only four patients were truly lost to follow up. For the purpose of analysis, the last two categories were considered to be "lost to follow up".

Table 1 shows the types of cyanotic congenital heart disease in this study. Table 2 shows the mortality on six months follow up if the patients who were "lost to follow up" were excluded. The mortality among the patients with low available oxygen or oxygen unloading capacity was much higher (76·2% and 54·5%, respectively) compared with those with normal available oxygen or oxygen unloading capacity (10·7% and 6·3%, respectively), the difference being statistically very significant (p<0·000 000 01 and p<0·000 01, respectively). In contrast, mortality was not significantly higher among the children with haemoglobins of 18 g/dl and above, or haematocrits above 65%, compared with the corresponding groups (p>0·71 and p>0·33, respectively). Children with arterial oxygen saturations of 60% and below did show an increased mortality compared with those with arterial oxygen saturation above 60% (p<0·003). Arterial oxygen content (<150 ml/l) was a useful prognostic criterion but not as good as available oxygen.

Actuarial analysis with maximum use of the data[13] (children who were "lost to follow up" can also contribute some information) was carried out (Table 3). The children with low available oxygen, low oxygen unloading capacity, and low arterial oxygen saturation showed a significantly lower six month survival rate compared with those with normal indices (p<0·001 in all three instances). Again, arterial oxygen content was a useful prognostic criterion but inferior to available oxygen. As before, children with haemoglobin 18 g/dl and above did not show a decreased survival rate compared with those with haemoglobins below 18 g/dl (p>0·70). Patients with haematocrits above 65% had a lower survival rate compared with those with haematocrits of 65% and below (p<0·02).

Table 1 *Types of cyanotic congenital heart disease*

Diagnosis	*Total No.*	*Not op.*	*Op.*	*↓AO$_2$*	*Normal AO$_2$*	*↓O$_2$UC*	*Normal O$_2$UC*
Fallot's tetralogy	25	10	15	5	20	12	13
Transposition of great arteries	16	15	1	6	10	12	4
Pulmonary atresia ±VSD	12	9	3	3	9	7	5
Pulmonary stenosis with right-to-left shunt via ASD/VSD	10	6	4	2	8	5	5
Eisenmenger's syndrome	5	5	0	5	0	5	0
Double outlet right ventricle	3	2	1	0	3	0	3
Total anomalous pulmonary venous drainage	3	3	0	2	1	3	0
Tricuspid atresia	2	1	1	2	0	2	0
Ebstein's anomaly	2	2	0	1	1	2	0
Single atrium, cleft mitral valve, mitral regurgitation	1	0	1	0	1	0	1
Total	79	53	26	26	53	48	31

VSD, ventricular septal defect; ASD, atrial septal defect; Op., operated; AO$_2$, available oxygen; O$_2$UC, oxygen unloading capacity.

Table 2 *Mortality on six month follow up (patients who were "lost to follow up" were excluded)*

Variable		*Mortality on 6 month follow up*		*Significance of difference*
Low AO$_2$	≤9·6 ml/dl	16/21	76·2%	p<0·000 000 01
Normal AO$_2$	>9·6 ml/dl	3/28	10·7%	
Low O$_2$UC	≤2·0 ml/dl	18/33	54·5%	p<0·000 01
Normal O$_2$UC	>2·0 ml/dl	1/16	6·3%	
Haemoglobin	≥18 g/dl	6/14	42·9%	p>0·71
	<18 g/dl	13/35	37·1%	
Haematocrit	>65%	3/5	60·0%	p>0·33
	≤65%	13/35	37·1%	
Arterial oxygen saturation	≤60%	7/9	77·8%	
	>60%	12/40	30·0%	p<0·003
	≤55%	4/4	100%	
	>55%	15/45	33·3%	p<0·000 1
	≤70%	10/16	62·5%	
	>70%	9/33	27·3%	p<0·05
Arterial oxygen content	<150 ml/l	12/15	80·0%	
	≥150 ml/l	7/34	20·6%	p<0·000 01

Note: (a) The haematocrit values of nine of the patients were not available.
(b) AO$_2$, available oxygen; O$_2$UC, oxygen unloading capacity.

Table 3 *Six month survival rates (actuarial analysis with maximum use of data)*

Variable		*No.*	*6 month survival rate*	*Standard error*	*Significance of difference*
Low AO$_2$	≤9·6 ml/dl	26	0·24	0·11	t=36·78 (77df)
Normal AO$_2$	>9·6 ml/dl	53	0·90	0·05	p≤0·001
Low O$_2$UC	≤2·0 ml/dl	48	0·49	0·09	t=27·34 (77df)
Normal O$_2$UC	>2·0 ml/dl	31	0·96	0·04	p≤0·001
Haemoglobin	≥18 g/dl	25	0·68	0·14	t=0·38 (77df)
	<18 g/dl	54	0·67	0·09	p>0·70
Haematocrit	>65%	10	0·57	0·20	t=2·57 (62df)
	≤65%	54	0·67	0·09	p<0·02
Arterial oxygen saturation	≤60%	13	0·28	0·16	t=16·82 (77df)
	>60%	66	0·74	0·07	p≤0·001
	≤55%	9	0·19	1·20	t=3·45 (77df)
	>55%	70	0·70	0·08	p=0·001
	≤70%	27	0·43	0·35	t=6·71 (77df)
	>70%	52	0·78	0·09	p<0·001
Arterial oxygen content	<150 ml/l	23	0·23	0·61	t=7·27 (77df)
	≥150 ml/l	56	0·84	0·07	p<0·001

Note: (a) The haematocrit results of some of the patients were not available.
(b) df, degrees of freedom; AO$_2$, available oxygen; O$_2$UC, oxygen unloading capacity.

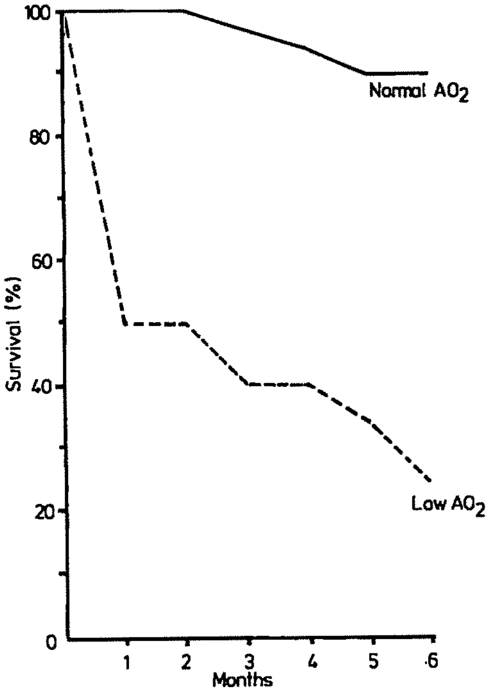

Fig. 1

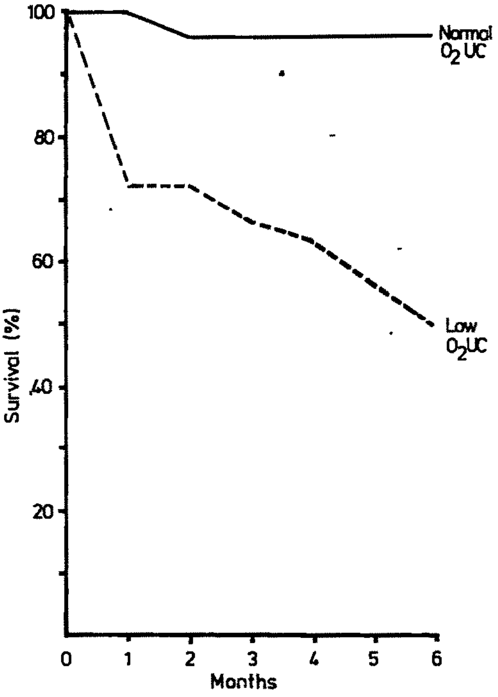

Fig. 2

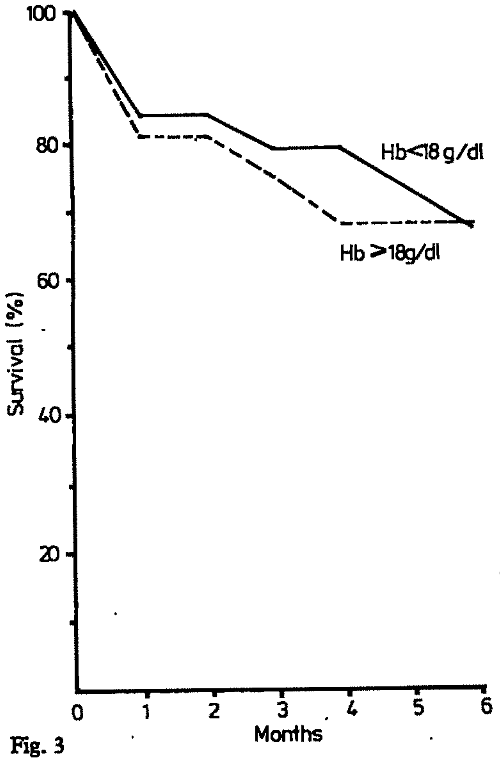

Fig. 3

Fig. 1 *Six month survival of patients with normal (>9·6 ml/dl) and low (≤9·6 ml/dl) available oxygen (AO_2). Only 24% of patients with low AO_2 survived six months, in contrast to 90% of those with normal AO_2 ($p<0\cdot001$).*

Fig. 2 *Six month survival of patients with normal (>2·0 ml/dl) and low (≤2·0 ml/dl) oxygen unloading capacity (O_2UC). Only 49% of patients with low O_2UC survived six months, in contrast to 96% of those with normal O_2UC ($p<0\cdot001$).*

Fig. 3 *Six month survival of patients with haemoglobin (Hb) ≥18 g/dl and Hb <18g/dl. There is no significant difference between the two groups ($p>0\cdot70$).*

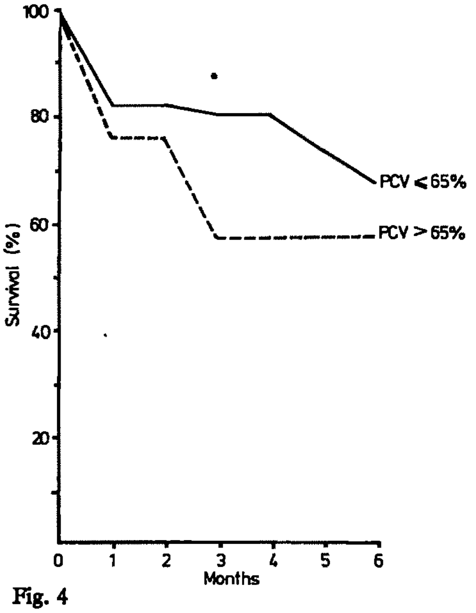

Fig. 4

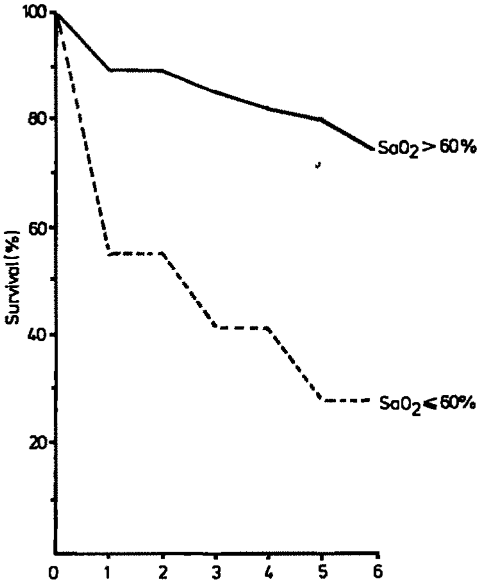

Fig. 5

Fig. 4 *Six month survival of patients with haematocrit PCV >65% and PCV ≤65%. Though the difference is statistically significant ($p<0{\cdot}02$), it is not large enough to enable haematocrit to become a useful prognostic criterion.*

Fig. 5 *Six month survival of patients with arterial oxygen saturation (SaO_2) >60% and SaO_2 ≤60%. Though the difference between the two groups is very obvious ($p\leq0{\cdot}001$), SaO_2 will have a serious disadvantage if used as a prognostic criterion, because only 74% of those with SaO_2 >60% will be alive at six months.*

Inspection of the magnitude of the Student's t values (Table 3) shows that available oxygen and oxygen unloading capacity are likely to be more useful as prognostic criteria for survival at six months than the arterial oxygen saturation, arterial oxygen content, haemoglobin, or haematocrit. Fig. 1 to 5 show these conclusions in graphic form. It appears that available oxygen is the best prognostic criterion for survival at six months. Arterial oxygen saturation will have a serious disadvantage if it is used as a prognostic criterion (that is, if only patients with a low arterial oxygen saturation (60% and below) are selected for surgery): only 74% of patients with arterial oxygen saturations above 60% will be alive at six months, unoperated, compared with 90% for those with normal available oxygen and 96% for those with normal oxygen unloading capacity. The cut off point for arterial oxygen saturation at 60% was chosen arbitrarily. If 55% and 70%, however, are also chosen as cut off points, the above conclusions remain valid (see Tables 2, 3, 4). Haemoglobin and haematocrit appear to be useless as prognostic criteria. The predictive value for survival at six months for the six variables is shown in Table 4.

Discussion

This study is the first report, as far as we are aware, of the use of available oxygen and oxygen unloading capacity as prognostic criteria in children with cyano-

Table 4 *Predictive value for survival at six months (for patients with complete follow up)*

Variable		*Total No.*	*No. survived*	*Predictive value*
Available oxygen	>9·6 ml/dl	28	25	89·3%
Oxygen unloading capacity	>2·0 ml/dl	16	15	93·7%
Haemoglobin	<18·0 g/dl	35	22	62·9%
Haematocrit	≤65·0%	35	22	62·9%
Arterial oxygen saturation	>60%	40	28	70·0%
	>55%	45	30	66·7%
	>70%	33	24	72·7%
Arterial oxygen content	≥150 ml/l	34	27	79·4%

Table 5 *Comparison of "complete follow up" and "lost to follow up" groups*

Variable	*Complete follow up**			*Lost to follow up†*			*Significance of difference*
	No.	*Mean*	*SD*	*No.*	*Mean*	*SD*	
Available oxygen (AO_2)	49	9·8	3·6	30	10·3	4·2	$p>0\cdot05$
Oxygen unloading capacity (O_2UC)	49	0·4	3·3	30	0·3	3·9	$p>0\cdot05$
Haemoglobin	49	16·7	3·1	30	17·7	3·5	$p>0\cdot05$
Haematocrit	40	51·5	10·4	24	55·7	12·0	$p>0\cdot05$
Arterial oxygen saturation	49	74·1	13·9	30	72·1	14·0	$p>0\cdot05$

*Follow up for six months (includes those who were not operated on during the six months after cardiac catheterisation, or those who died before operation).
†"Lost to follow up" usually the result of operation within six months of cardiac catheterisation (only four patients were truly lost to follow up).
SD, standard deviation.

tic congenital heart disease. The results appear to be very promising, and these indices would be very useful in helping the physician to decide on the urgency of cardiac catheterisation and surgery in a particular patient.

Comparison is made between available oxygen and oxygen unloading capacity and other physiological indices (arterial oxygen saturation and content, haemoglobin, haematocrit) to assess their value in prognosis. Haemoglobin and haematocrit were found to be useless as prognostic criteria. On theoretical grounds, both available oxygen and oxygen unloading capacity have a distinct advantage over arterial oxygen saturation as indices of oxygen availability to the tissues, since the haemoglobin and haemoglobin-oxygen affinity are used in addition to the arterial oxygen saturation in the calculation of these two indices. They are also expected to be superior to arterial oxygen content, since the latter does not take into account haemoglobin-oxygen affinity (p 50 in vivo). These theoretical expectations were fulfilled by our results which showed the distinct superiority of available oxygen and oxygen unloading capacity as prognostic criteria over the arterial oxygen saturation and content. As may be expected, arterial oxygen content was better than arterial oxygen saturation in prognosis because the former uses the haemoglobin in addition to the oxygen saturation.

The oxygen unloading capacity is calculated[7] from the haemoglobin, arterial oxygen saturation, and the oxygen saturation of blood for a venous oxygen tension of 40 mmHg. The choice of 40 mmHg as the venous oxygen tension for this calculation is based on the normal value for resting normal subjects. Jones *et al.*[8] argued on mathematical and functional grounds, that using 20 mmHg as the venous oxygen tension instead of 40 mmHg in the calculation of the capacity to unload oxygen will result in a more realistic index, the available oxygen. Our observation that available oxygen is a better prognostic criterion than oxygen unloading capacity is a demonstration of the validity of the theoretical arguments.

To determine whether the patients who are "lost to follow up" (largely as the result of operation) are any different from those with "complete follow up", the distribution of the available oxygen, oxygen unloading capacity, haemoglobin, haematocrit, and arterial oxygen saturation in both these groups are compared (Table 5). (The specific congenital defects in the operated and non-operated groups are shown in Table 1.) Our results show that for each of these five variables, there is no statistically significant difference between the two groups ($p>0\cdot05$). Thus our conclusions appear to be essentially valid despite the patients "lost to follow up" as the result of surgery.

In summary, available oxygen and oxygen unloading capacity appear to be valuable and promising prognostic criteria for children with cyanotic congenital heart disease. Like other prognostic criteria, these variables should be used in conjunction with all other clinical and laboratory data, such as growth failure, presence or absence of hypercyanotic spells, requirements for cardiac decongestive drugs, findings at cardiac catheterisation and angiography, and so on. Since available oxygen and oxygen unloading capacity by themselves are better prognostic criteria than the haemoglobin, haematocrit, and arterial oxygen saturation or content when used alone, it appears reasonable to expect that when used together with the clinical and laboratory data, they will still prove to be superior to the other three variables when they are also used in conjunction with the same data. In any case, the physician can have two new criteria, in addition to all other conventional criteria, whereby he may assess the prognosis of a child with cyanotic congenital heart disease.

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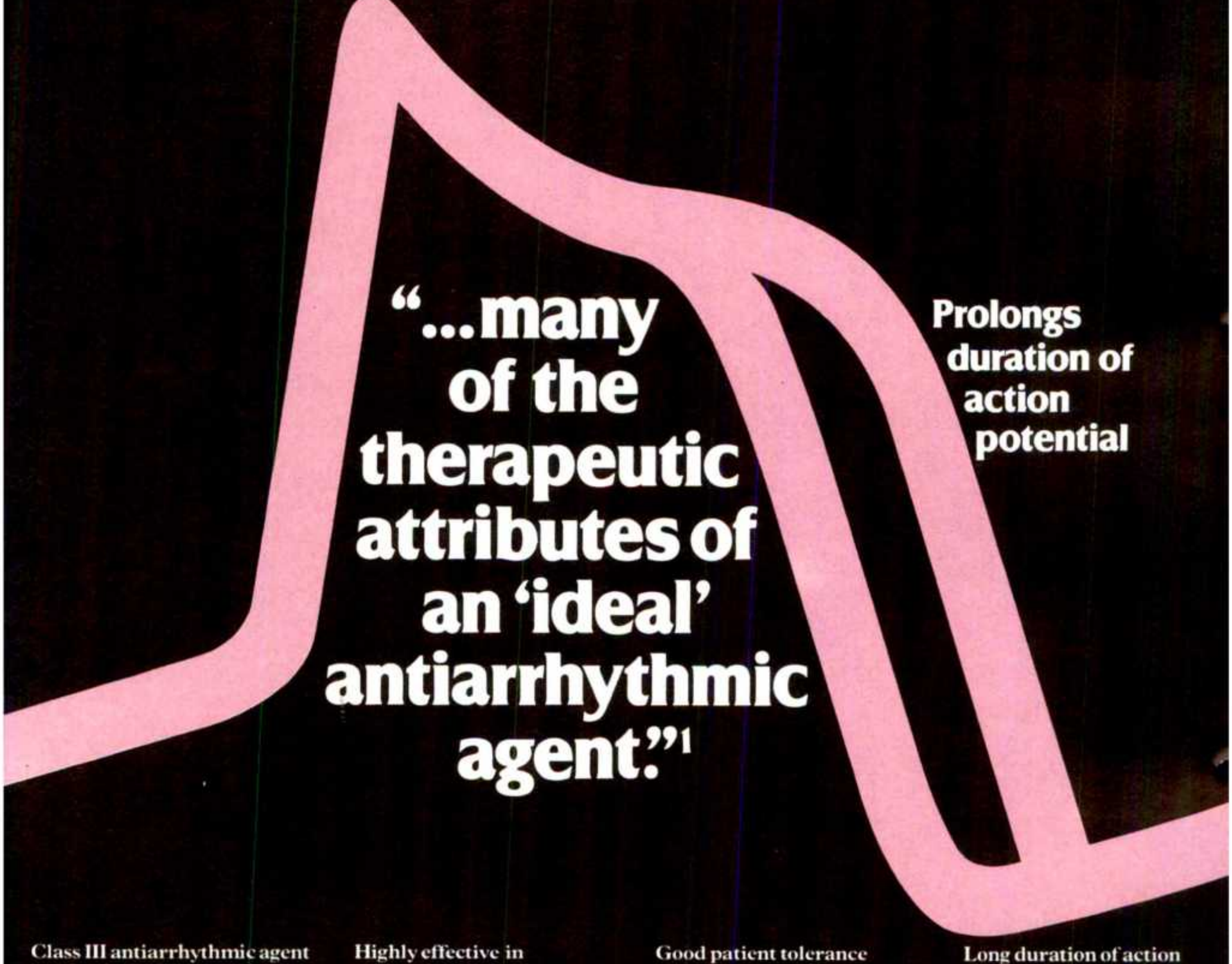
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Effects of renal transplantation on left ventricular size and function

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SUMMARY Thirteen patients with chronic renal failure and uraemia were investigated by echocardiography preoperatively before and after haemodialysis and again after a successful renal transplantation to evaluate the cardiac changes caused by renal transplantation.

After renal transplantation, the left ventricular end-diastolic and end-systolic diameters, as well as the cardiac index, decreased, probably because of the decreased left ventricular filling pressure. The left ventricular wall thickness and mass decreased, apparently as a result of the decrease of the left ventricular preload and also of the decrease of the afterload, because the systolic blood pressure decreased. The left atrial diameter decreased in response to the decreased left ventricular preload and wall hypertrophy.

The changes in the indices of left ventricular function as a result of haemodialysis appeared to predict the changes seen after renal transplantation.

Renal transplantation appears to have a tendency to result in normal left ventricular and left atrial volumes, as well as to lessen left ventricular hypertrophy, without significantly improving left ventricular function.

In chronic renal failure the heart and circulation are affected by several pathological conditions. Increased oxygen demand of the tissues, chronic volume overload, and anaemia, in addition to the presence of an artificial arteriovenous fistula, increase cardiac output, leading to left ventricular dilatation and increased cardiac size.[1-6] In uraemic patients pronounced left ventricular hypertrophy often occurs principally because of arterial hypertension,[6] which is frequently severe and difficult to control adequately. Uraemic changes in tissue metabolism and electrolyte balance may also affect cardiac function, leading to uraemic pericarditis[1 7 8] and even possibly to uraemic cardiomyopathy.[9 10]

Renal transplantation corrects the uraemic metabolic changes and restores the decreased blood haemoglobin concentrations to normal, and often, at least partially, returns the increased blood pressure to normal. Hence restoration of the circulation and cardiac function is expected, and, indeed, cardiac size has been found to decrease,[11 12] as has left ventricular size and cardiac output.[2] In a previous study we investigated the cardiac effects of haemodialysis,[6] and the purpose of the present study was to investigate, by echocardiography, the cardiac changes caused by renal transplantation, especially its effect on left ventricular size and function. We also wanted to investigate the extent to which the changes occurring after renal transplantation could be predicted by the acute cardiac changes seen after haemodialysis.

Patients and methods

Nine male and four female patients with chronic renal failure and uraemia, comprising the consecutive cases of successful renal transplantation, were investigated before and after haemodialysis, an average of four and a half months before renal transplantation and again at a mean of a little over nine months after transplantation. The transplant was considered to function well when the serum creatinine level remained below 150 μmol/l without haemodialysis. The ages of the patients ranged from 20 to 50 years, with a mean age of 31 years. Ten of the patients were hypertensive and three were normotensive. Antihypertensive treatment usually consisted of diuretic, beta-blocking, and vaso-

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dilating drugs. The cause of chronic renal failure was glomerulonephritis in 10 patients, interstitial nephritis in one, hydronephrosis in one, and renal amyloid disease in one. All the patients had an arteriovenous fistula in either upper extremity, constructed by the same surgeon, in studies performed both before and after renal transplantation. All the patients were treated by corticosteroids and immunosuppressive drugs after transplantation. None of the patients had a history of myocardial infarction or evidence of coronary artery disease. Before transplantation all the patients were treated by haemodialysis lasting four hours three times a week.

The echocardiographic examinations were made immediately before and within 30 minutes of haemodialysis. Echocardiograms were obtained with an ATL Mark III real-time echocardiographic system using a mechanical sector transducer with a 90° angle and a frequency of 3.0 megaHertz. The M-mode echocardiogram, electrocardiogram, and carotid pulse tracing were recorded with a Honeywell fibreoptic recorder equipped with a black and white adapter using 3M-dry silver paper and 50 mm/s paper speed. In the initial studies, a Picker Echoview ultrasonoscope equipped with a Polaroid film recorder was used. Echocardiograms were recorded by the same echocardiographer (MI) using an accurate standard technique[13] routinely employed in this laboratory.[14] The left ventricular end-diastolic diameter (LVDd) and wall thicknesses were measured at the point of the R wave in the electrocardiogram. The left ventricular volumes were calculated using the prolate ellipse formula, and the cardiac output was calculated as the product of the left ventricular stroke volume and the heart rate. The fractional shortening of the left ventricular minor axis in systole (FS) was calculated as (LVDd-LVDs)/LVDd × 100, where LVDs is left ventricular end-systolic diameter. The mean velocity of the left ventricular circumferential muscle fibre shortening (mVCF) was calculated as previously described,[15] using in the calculation the left ventricular ejection time measured from the simultaneously recorded carotid pulse tracing. The left ventricular mass was determined using LVDd and the mean value of the left ventricular posterior wall and interventricular septal thicknesses according to the formula previously established.[16]

Student's paired t test was used in analysing the differences between the results of serial studies. Two-variable linear regression estimates were used in the correlation studies.

Results

In no patients were the left ventricular contractions found to be asymmetric in real-time two dimensional studies. In three patients before, and in one patient after renal transplantation, a slight pericardial effusion was found, which did not seem to disturb cardiac function much.[17] Nine of the 10 patients with arterial hypertension before transplantation also needed antihypertensive drugs after operation, though in reduced amounts.

The renal transplantation did not cause significant changes in body weight, diastolic blood pressure, heart rate, left ventricular ejection time, fractional shortening, or mean velocity of left ventricular circumferential muscle fibre shortening compared with the measurements made either before or after haemodialysis treatment (Tables 1 and 2).

CHANGES VS MEASUREMENTS MADE BEFORE HAEMODIALYSIS (Tables 1 and 2)

As a result of the renal transplantation, the systolic blood pressure decreased by 19·6 ± 28·2 mmHg ($p < 0{\cdot}05$), the serum potassium concentration decreased by 1·7 ± 1·1 mmol/l ($p < 0{\cdot}001$), the serum urea concentration decreased by 21·1 ± 7·1 mmol/l ($p < 0{\cdot}001$), and the blood haemoglobin concentration increased by 61·5 ± 33·6 g/l ($p < 0{\cdot}001$). In our laboratory the normal range of serum potassium concentrations is 3·5 to 5·3 mmol/l and that of serum urea is 2·5 to 6·0 mmol/l.

The echocardiographic measurements showed the

Table 1 *Physical and laboratory data*

	Before haemodialysis	*After haemodialysis*	*After transplantation*	*P value*	
				BH vs AT	*AH vs AT*
Body weight (kg)	62·7 ± 8·1	61·2 ± 8·6	63·2 ± 8·9	NS	NS
Blood pressure (mmHg)					
Systolic	170·0 ± 33·6	156·2 ± 31·0	150·2 ± 25·9	0·05	NS
Diastolic	95·4 ± 16·6	86·2 ± 13·3	94·2 ± 11·9	NS	NS
Heart rate (bt/min)	76·8 ± 14·4	77·7 ± 14·5	71·3 ± 9·1	NS	NS
LVET (ms)	279 ± 24	266 ± 26	270 ± 21	NS	NS
Blood haemoglobin (g/l)	61·5 ± 14·1		122·9 ± 27·1	0·001	
Serum potassium (mmol/l)	5·54 ± 0·96	3·81 ± 0·29	3·84 ± 0·62	0·001	NS
Serum urea (mmol/l)	28·8 ± 7·4	12·5 ± 4·3	7·6 ± 2·7	0·001	0·001

Mean ± standard deviation. BH, before haemodialysis; AH, after haemodialysis; AT, after renal transplantation; LVET, left ventricular ejection time; n = 13.

Table 2 *Echocardiographic data*

	Before haemodialysis	*After haemodialysis*	*After transplantation*	*P value*	
				BH vs AT	*AH vs AT*
Left atrial diameter (mm)	41·4 ± 4·3	38·5 ± 5·9	35·8 ± 4·5	0·005	NS
Cardiac index (l/min per m²)	5·65± 1·05	5·41± 1·31	3·94± 1·48	0·005	0·01
Left ventricle					
End-diastolic diameter (mm)	56·6 ± 4·4	54·2 ± 3·4	49·6 ± 5·9	0·001	0·01
End-systolic diameter (mm)	39·3 ± 4·8	36·4 ± 3·3	32·8 ± 6·1	0·005	0·05
Fractional shortening (%)	30·6 ± 5·3	32·9 ± 4·3	34·3 ± 7·1	NS	NS
mVCF (circ/s)	1·09± 0·20	1·24± 0·19	1·25± 0·24	NS.	NS
Posterior wall thickness (mm)	13·2 ± 2·1	13·2 ± 1·9	12·2 ± 2·3	0·05	0·05
Mass index (g/m²)	197·7 ± 44·8	178·2 ± 36·8	143·5 ± 47·3	0·001	0·01

Mean ± standard deviation. BH, before haemodialysis; AH, after haemodialysis; AT, after renal transplantation; mVCF, mean velocity of the circumferential muscle fibre shortening; n = 13.

left atrial diameter to have decreased by 5·5 ± 5·4 mm ($p < 0·01$) (Fig. 1), left ventricular end-diastolic diameter to have decreased by 7·0 ± 5·1 mm ($p < 0·001$), left ventricular end-systolic diameter to have decreased by 6·5 ± 6·7 mm ($p < 0·005$) (Fig. 2), and the cardiac index to have decreased by 1·7 ± 1·7 l/min per m^2 ($p < 0·005$) (Fig. 3). Renal transplantation also caused a significant reduction in left ventricular hypertrophy: the left ventricular posterior wall thickness decreased by 1·1 ± 1·7 mm ($p < 0·05$) and the left ventricular mass diminished by 54·2 ± 43·3 g/m^2 ($p < 0·001$).

The patients' ages correlated negatively with fractional shortening ($r = -0·679$, $p < 0·05$) and mean velocity of left ventricular circumferential muscle fibre shortening ($r = -0·632$, $p < 0·05$) measured before haemodialysis.

CHANGES VS MEASUREMENTS MADE AFTER HAEMODIALYSIS (Tables 1 and 2)
After renal transplantation, the serum urea concentration decreased by 4·8 ± 3·3 mmol/l ($p < 0·001$) and, by echocardiographic measurement, left ventricular

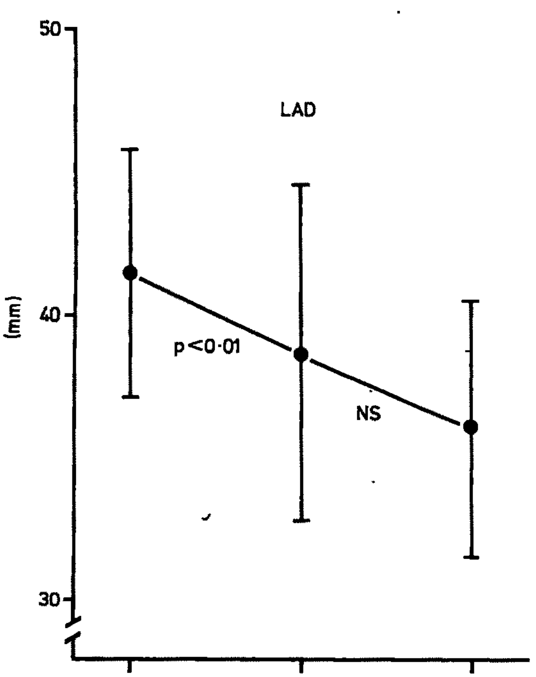

Fig. 1 *The effect of haemodialysis (HD) and renal transplantation (TR) on left atrial diameter (LAD).*

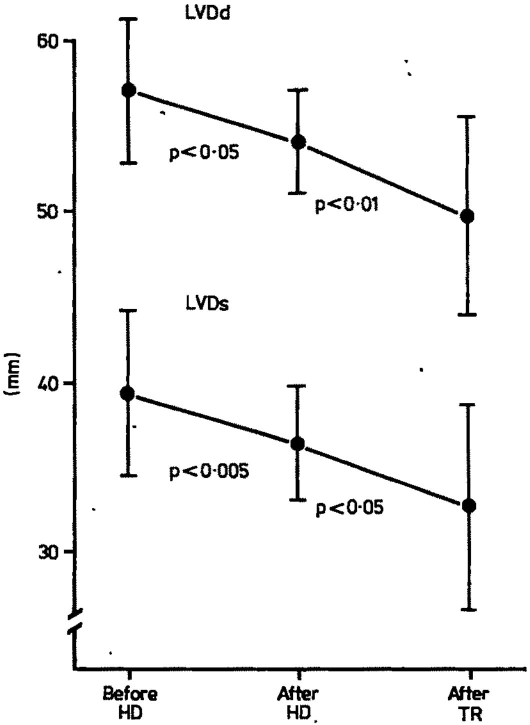

Fig. 2 *The effect of haemodialysis (HD) and renal transplantation (TR) on left ventricular end-diastolic (LVDd) and end-systolic (LVDs) diameters.*

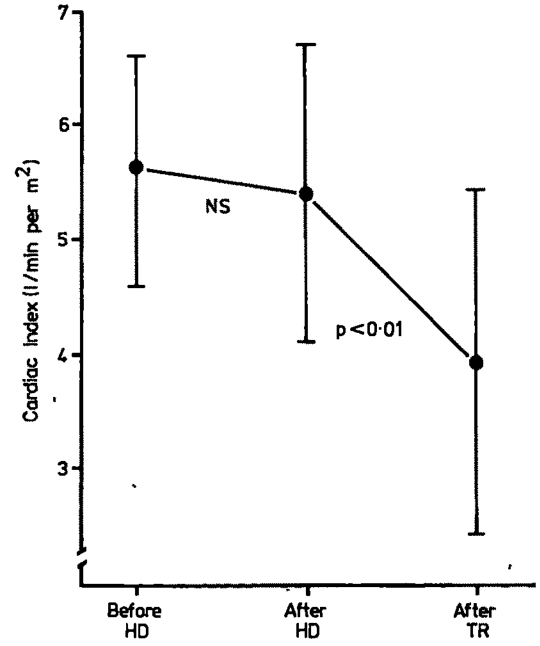

Fig. 3 *The effect of haemodialysis (HD) and renal transplantation (TR) on cardiac index.*

end-diastolic diameter decreased by 4·6 ± 4·4 mm ($p < 0.01$) (Fig. 2), left ventricular end-systolic diameter decreased by 3·5 ± 5·2 mm ($p < 0.05$) (Fig. 2), and the cardiac index decreased by 1·5 ± 1·7 l/min per m^2 ($p < 0.01$) (Fig. 3).

CORRELATIONS BETWEEN CHANGES SEEN AFTER RENAL TRANSPLANTATION

The changes in the measurements made before haemodialysis and after renal transplantation were evaluated. The changes in the measurements as a result of renal transplantation did not correlate with the time between the operation and the postoperative measurement. There was a significant positive correlation between the changes in systolic blood pressure and left ventricular end-systolic diameter ($r = 0.590$, $p < 0.05$). The systolic blood pressure measured before haemodialysis correlated positively with its decrease because of the renal transplantation ($r = 0.662$, $p < 0.05$) and the diastolic blood pressure with its change ($r = 0.746$, $p < 0.01$). The changes in systolic blood pressure correlated negatively with the changes in fractional shortening ($r = -0.607$, $p < 0.05$) and in mean velocity of left ventricular circumferential muscle fibre shortening ($r = -0.746$, $p < 0.01$). The changes in the left atrial diameter correlated positively with the changes in left ventricular end-diastolic diameter ($r = 0.722$, $p<0.01$) and with the changes in the left ventricular mass ($r = 0.588$, $p < 0.05$). The changes in the cardiac index correlated positively with the changes in the left ventricular mass ($r = 0.736$, $p < 0.01$).

PREDICTIVE VALUE OF CHANGES RESULTING FROM HAEMODIALYSIS

The changes in body weight caused by haemodialysis correlated positively with the changes caused by the renal transplantation as regards the systolic blood pressure ($r = 0.674$, $p < 0.05$) and diastolic blood pressure ($r = 0.572$, $p < 0.05$). This correlation was negative as regards the changes in fractional shortening ($r = -0.617$, $p < 0.05$). The changes in the diastolic blood pressure as a result of haemodialysis correlated with the changes in the left atrial diameter caused by the renal transplantation ($r = 0.622$, $p < 0.05$). The haemodialysis changes of left ventricular end-systolic diameter correlated negatively with the transplantation changes in mean velocity of left ventricular circumferential muscle fibre shortening ($r = -0.604$, $p < 0.05$) and the haemodialysis changes of fractional shortening correlated positively with the transplantation changes of fractional shortening ($r = 0.582$, $p < 0.05$) and mean velocity of left ventricular circumferential muscle fibre shortening ($r = 0.738$, $p < 0.01$). The haemodialysis changes in the latter predicted its changes after transplantation ($r = 0.733$, $p < 0.01$), and the haemodialysis changes of the cardiac index predicted the changes in left ventricular posterior wall thickness ($r = 0.593$, $p < 0.05$) caused by renal transplantation, but not the changes in left ventricular mass.

Discussion

Normal blood haemoglobin and serum potassium concentrations as well as nearly normal serum urea concentration after renal transplantation showed that the procedure corrected the abnormal metabolic and electrolyte balance. This was associated with the disappearance of hypervolaemia and hence a decrease in the left ventricular filling pressure. The serum potassium concentrations were at the low end of the normal range, perhaps because of diuretic and corticosteroid treatment. Unlike haemodialysis,[2 6 18] renal transplantation did not cause a significant reduction in body weight because, in spite of the decrease of water retention and thus extracellular volume, the muscle and fat tissue apparently increased as a result of normal metabolism and also corticosteroid treatment. Though the diastolic blood pressure did not change significantly, the systolic blood pressure decreased after renal transplantation, indicating a decreased left ventricular afterload. Though the arteriovenous fistula was left open after transplantation as a reserve for possible future complications, both the left ventricular preload and afterload seemed to decrease as a result of operation, and hence changes in the echocardiographic measurements were expected.

The mean left ventricular diameter decreased both in systole and diastole, reaching normal values, so that the cardiac index also decreased significantly because of the decreased left ventricular preload. The mean cardiac index, however, still remained high because of the open arteriovenous fistula. The correction of anaemia also resulted in decreased cardiac output because of increased viscosity and improved oxygen carrying capacity of the blood. In spite of the decreased preload and thus decreased Starling's effect, and in spite of the increased blood viscosity, the indices of left ventricular function showed a tendency to increase, though not significantly, which means that the decreasing effect of the reduced left ventricular preload on left ventricular function was compensated for by the decreased afterload and increased ventricular contractility, perhaps because of the mechanical advantage of a smaller heart rather than because of favourable changes in metabolism and electrolyte balance. The changes in left ventricular volumes and function found in the present study are in agreement with the findings of Riley *et al.*[2] in four patients. Decreases in the cardiac volume[11] and cardiothoracic ratio[12] measured from chest *x*-rays have also been found after renal transplantation.

The left ventricular wall thickness and mass decreased significantly after renal transplantation because of decreased cardiac output and decreased ventricular afterload. Hypertension is obviously the most important factor in causing left ventricular hypertrophy in chronic renal failure.[6] Though the cause of increased blood pressure is undoubtedly renal in patients with chronic renal failure, hypertension seems to be frequently, at least partially, irreversible. Possible causes for this are postoperative steroid therapy, the influence of the patient's own kidneys, and chronic rejection.[19] Only in one of our patients was hypertension entirely cured after transplantation and this was one of the two patients whose own kidneys were removed. Because of residual hypertension and also because of the open arteriovenous fistula, the left ventricular wall thickness and mass still remained greater than normal. The extreme left ventricular hypertrophy may also be partially irreversible even though its cause is removed. Because the effect of the renal transplantation seemed to be greater on the left ventricular preload than on the afterload, it is not surprising that the changes in blood pressure did not correlate significantly with the changes in left ventricular wall thickness or mass. On the other hand, the changes in systolic blood pressure correlated well with the changes of left ventricular end-systolic diameter, fractional shortening, and mean velocity of left ventricular circumferential muscle fibre shortening, reflecting the significance of afterload on left ventricular function, on which also the modern vasodilator treatment of cardiac failure is based.

The left atrial diameter also decreased significantly after renal transplantation and its changes correlated significantly with the changes in left ventricular diastolic volume and mass. In previous studies we found that the left atrial size depended on the degree of left ventricular hypertrophy and therefore also on the decreased left ventricular diastolic compliance.[6 20] As the changes in left ventricular mass are dependent on the changes in preload and afterload, both of which have an effect on cardiac output, the correlation between the changes in left ventricular mass and cardiac index was to be expected.

PREDICTIVE VALUE OF CHANGES CAUSED BY HAEMODIALYSIS

As haemodialysis causes a very acute decrease in left ventricular preload,[2 6 18] it was of interest to discover which variables, if any, could predict the cardiac changes caused by renal transplantation. The effect of haemodialysis on left ventricular afterload appears to be less than on preload, because in our previous work haemodialysis caused a significant decrease only in diastolic blood pressure.[6] The correlations seen between the changes in body weight or diastolic blood pressure resulting from haemodialysis and the changes caused by renal transplantation were slight and have no obvious explanation. The decrease in water loss and hence body weight after haemodialysis is adjustable and so perhaps greater in patients with more advanced renal disease and hypertension; in these patients, renal transplantation perhaps also causes a more distinct decrease in blood pressure and a subsequent increase in left ventricular function.

On the other hand, however, the changes in left ventricular end-systolic diameter and the indices of left ventricular function caused by haemodialysis more closely predicted the changes of left ventricular performance caused by renal transplantation. Hence measurement of the changes in left ventricular end-systolic diameter, fractional shortening, and mean velocity of left ventricular circumferential muscle fibre shortening caused by haemodialysis could be applicable in practice to predict the changes in left ventricular function after renal transplantation.

Renal transplantation thus apparently decreases left ventricular and left atrial volumes towards normal, and also lessens left ventricular hypertrophy, but it does not significantly improve left ventricular function. The changes in left ventricular end-systolic size and the indices of left ventricular function resulting from haemodialysis are apparently indicative of changes in left ventricular function caused by renal transplantation.

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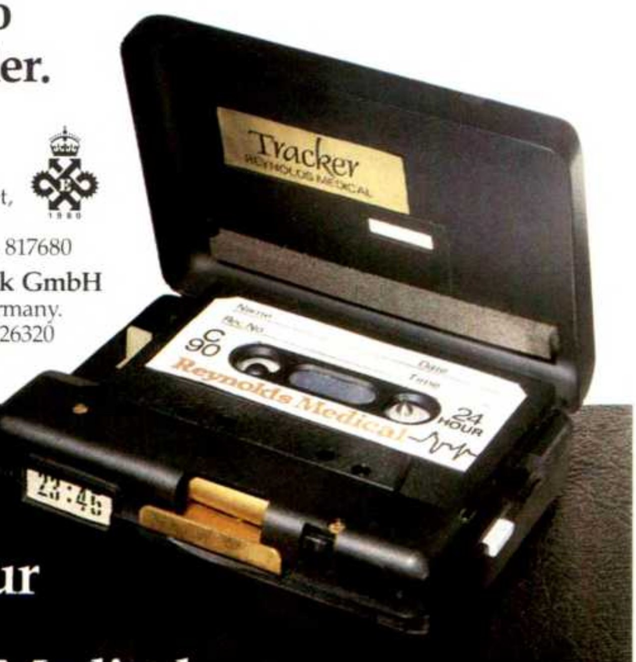

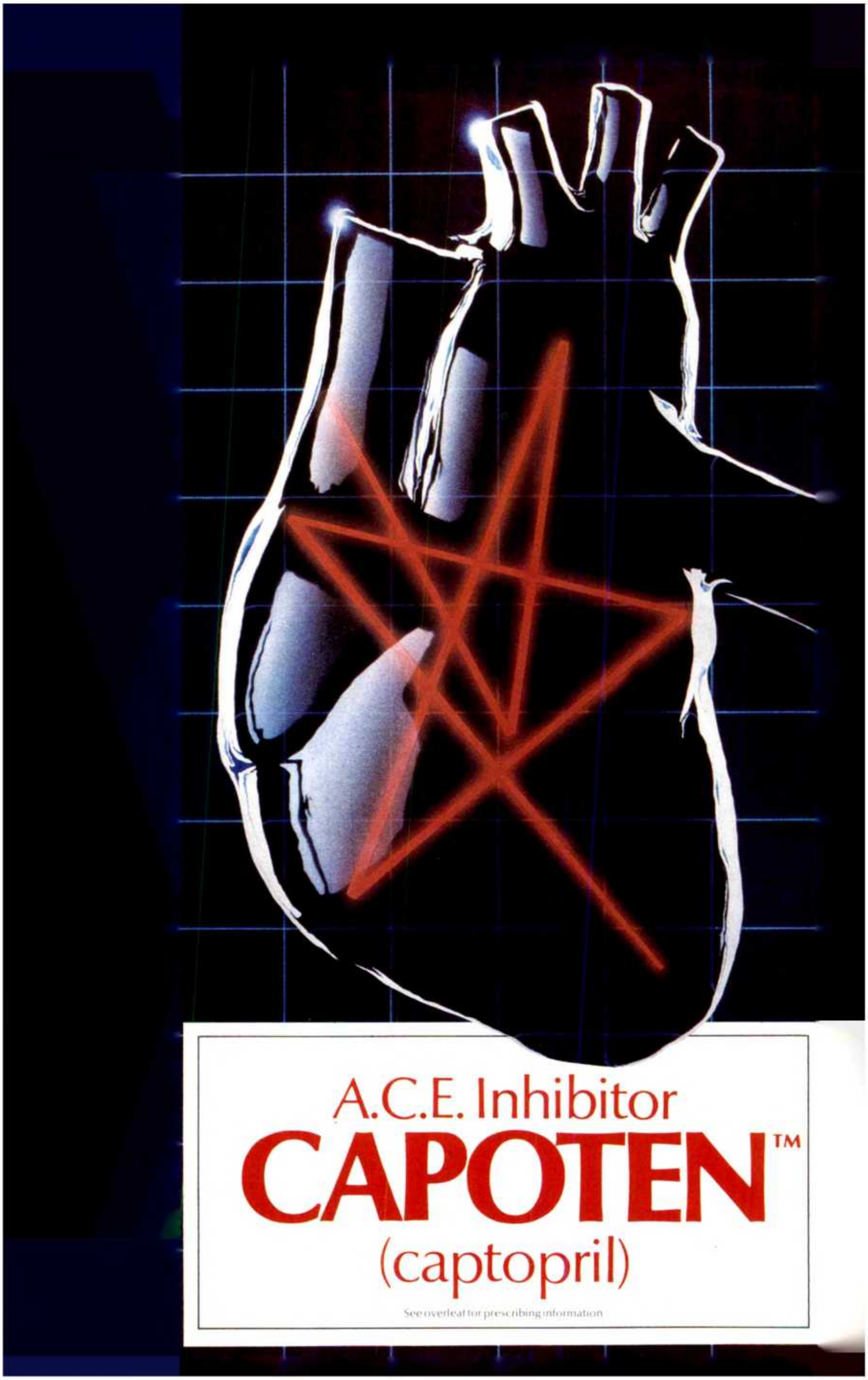

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CAPOTEN™ TABLETS Capoten tablets each contain 25 mg, 50 mg or 100 mg captopril. **USES** Capoten (captopril) in hypertension appears to lower blood pressure primarily by renin-angiotensin-aldosterone inhibition. Usage in hypertensive crises should be avoided. It has also been shown to be of benefit in the management of severe, treatment-refractory congestive heart failure. **Indications Hypertension** The treatment of severe hypertension where standard therapy has failed. **Congestive Heart Failure** Capoten is indicated for the treatment of severe, treatment-refractory congestive heart failure. The drug should be used together with diuretics and digitalis, but only after these agents have failed to produce a satisfactory response. **DOSAGE AND ADMINISTRATION** Capoten should be taken one hour before meals. **Adults Hypertension** The usual dose range of Capoten is 25-150 mg t.i.d. The maximum recommended daily dose is 450 mg. The initial daily dose of Capoten is 25 t.i.d. which should be increased to 50 mg t.i.d. if a satisfactory reduction of blood pressure has not been achieved in two weeks. If a satisfactory response has not been achieved after a further two weeks a modest dose of a thiazide diuretic (hydrochlorothiazide) or in patients with impaired renal function a loop diuretic (frusemide) should be added. The diuretic should be increased until a satisfactory response is obtained or its maximal dose is reached. Should Capoten 50 mg t.i.d. together with the diuretic fail to give a satisfactory reduction in blood pressure, then Capoten should be increased to 100 mg t.i.d., and then, if necessary, 150 mg t.i.d. For patients with accelerated or malignant hypertension, who are unresponsive to conventional therapy, it may be necessary to increase the daily dose of Capoten every 24 hours, until a satisfactory blood pressure response is obtained or the maximum dose of Capoten is reached. When Capoten is used alone, concomitant sodium restriction may be advantageous. Capoten may be used in conjunction with other antihypertensive agents, particularly thiazide diuretics and beta-blockers. **Congestive Heart Failure**. The usual starting daily dose is 25 mg t.i.d. and the usual effective dose range is between 25 and 150 mg t.i.d. After a dose of 50 mg t.i.d. is reached, further increases in dose should be delayed, where possible, for several weeks to determine if a satisfactory response occurs. Capoten should be used in conjunction with the highest usual doses of diuretic and with digitalis. Capoten therapy must be started in the hospital (see Warnings). A maximum daily dose of 450 mg of Capoten should not be exceeded. **Patients with Renal Impairment** About 75% of a given daily dose of Capoten is usually excreted in the urine; Capoten retention occurs in the presence of impaired renal function. The dosage interval should be increased as follows when creatinine clearance is below 75 ml/min/1.73 m^2:

Creatinine Clearance (ml/min 1.73 m^2)	Dosage Interval (Hours)
>75	8
75-35	12-24
34-20	24-48
19-8	48-72
7-5	72-108 (3 to 4.5 days)

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Children Safety and effectiveness in children have not been established. Starting dose should be 1 mg per Kg bodyweight up to a maximum of 6 mg per Kg bodyweight divided into three doses per day. **CONTRA-INDICATIONS, PRECAUTIONS AND WARNINGS:- Contra-Indications** Previous hypersensitivity to Capoten **Warnings** NEUTROPENIA/AGRANULOCYTOSIS and PROTEINURIA have been reported in patients receiving Capoten. Urinary protein should be checked (dip stick) prior to treatment, monthly for 8 months and periodically thereafter. WBC should be carried out prior to treatment, fortnightly for three months and periodically thereafter. **Hypotension** A precipitous reduction of blood pressure may occasionally occur within the first three hours following the initial dose of Capoten in patients on diuretics, on a low sodium diet or undergoing dialysis. An exaggerated hypotensive effect may also occur with one or two subsequent doses. Medical supervision should be maintained for one hour after the initial dose. This transient hypotensive response is not a contra-indication to further doses which can be given without difficulty once blood pressure has increased after volume expansion. **Hypotension in Patients with Severe Congestive Heart Failure.** These patients, having either normal or low blood pressure, may experience marked falls in blood pressure, which have on rare instances been associated with arrhythmia or conduction defects, after the first few doses of Capoten. Because of the potential fall in blood pressure in these patients, therapy must be started in the hospital. Patients should be followed closely for the first two weeks of treatment and whenever the dose of Capoten and/or diuretic is increased. Patients treated for severe congestive heart failure should be warned to increase their physical activity slowly. **Serum Potassium** Since Capoten decreases aldosterone production, elevation of serum potassium may occur, especially in patients with renal failure. Potassium sparing diuretics or potassium supplements, if needed, should be used with caution, since they may lead to a significant increase in serum potassium. **Changes in Renal Function** Some patients with renal disease, particularly those with renal artery stenosis, have developed increased serum concentration of BUN and serum creatinine after reduction of blood pressure with Capoten, usually along with a diuretic. Capoten dosage reduction and/or discontinuation of diuretic may be required. For some of these patients, it may not be possible to normalise blood pressure and maintain adequate renal perfusion. **Pregnancy** The safety of Capoten in pregnancy has not been established. **Nursing Mothers** Exercise caution. **Surgery/Anaesthesia** In patients undergoing major surgery, or during anaesthesia with agents which produce hypotension, Capoten will block angiotensin II formation secondary to compensatory renin release. This may lead to hypotension which can be corrected by volume expansion. Capoten may cause a false-positive urine test for acetone. **Side Effects** Neutropenia/Agranulocytosis Proteinuria see Warnings. Skin rashes and taste disturbance have been reported. Gastric irritation and abdominal pain may occur. **Other** Paraesthesias of the hands, serum sickness, cough, bronchospasm and lymphadenopathy have been reported. Hypotension - see Warnings. Tachycardia has been observed in a few volume depleted patients. **Overdosage** In the event of overdosage, hypotension would be the most important problem. Volume expansion with an intravenous infusion of normal saline is the treatment of choice for restoring the blood pressure to normal. Capoten is removed by dialysis. **PACKAGE QUANTITIES** in bottles of 100. **Basic NHS Price** 25 mg tablets 100 - £21.40. **PRODUCT LICENCE NUMBERS, NAMES AND ADDRESSES Product Licence Numbers** Capoten tablets 25 mg PL 0034/0193;
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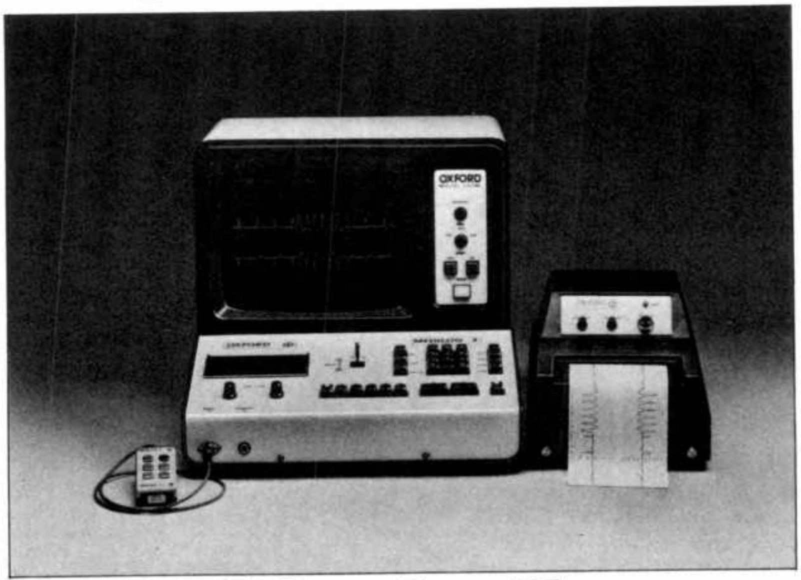

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Br Heart J 1982; 47: 161-6

Hyponatraemia as a marker for high renin heart failure

T BARRY LEVINE, JOSEPH A FRANCIOSA, THOMAS VROBEL, JAY N COHN

From the Department of Medicine, University of Minnesota Medical School, Minneapolis, Minnesota, USA

SUMMARY The factors that might activate the renin-angiotensin system in treated heart failure were explored. Serum Na^+ correlated inversely with plasma renin activity. The degree of congestive heart failure measured by right atrial pressure, pulmonary capillary wedge pressure, cardiac index, and systemic vascular resistance did not correlate with plasma renin activity. Similarly, renal function as measured by blood urea nitrogen, creatinine, and urinary Na^+ excretion did not correlate with plasma renin activity. In a prospectively screened group, seven patients with congestive heart failure who were found to be hyponatraemic had plasma renin activities greater than 15 ng/ml per h. Serial determinations in one patient showed plasma renin activity to vary inversely with the serum Na^+. It is concluded that serum sodium can be used to identify those patients with congestive heart failure who have a high plasma renin activity. The value of identifying these high renin heart failure patients was seen in their response in four cases to specific therapy with a converting enzyme inhibitor.

The renin-angiotensin system may play an important homeostatic role in both experimental and clinical congestive heart failure.[1-4] Increased circulating angiotensin II could contribute to systemic vasoconstriction which supports blood pressure[5 6] but also might adversely affect left ventricular performance.[7] Plasma renin activity has been reported to vary widely in patients with heart failure[2 8 9] but the mechanism of its stimulation and the reason it is raised in some patients but not in others is not understood.

Haemodynamics, renal function, or volume factors all might be expected to be capable of stimulating the renin-angiotensin system.[8 10-14] Since recent reports have shown a beneficial haemodynamic response in patients with heart failure to agents that block the activity of the renin angiotensin system,[2 15 16] an understanding of the factors that stimulate it in heart failure and the recognition of clinical correlates of high plasma renin activity might have important therapeutic implications.

In the present study we have explored the possible influence of haemodynamic and renal functional factors on plasma renin activity in a group of patients with moderate to severe heart failure, in hospital and carefully stabilised. The data confirm earlier work[8] that there is a strong negative correlation of plasma renin activity with serum sodium and indicate that the former does not correlate with other measured variables. Furthermore, a low serum sodium appears to be a fairly reliable guide to high plasma renin activity in heart failure.

Accepted for publication 17 September 1981

Subjects and methods

Forty-two patients underwent an extensive haemodynamic and renal evaluation. The patients were studied in a stable state after being in hospital for three to five days on a 43 or 86 mmol sodium and 100 mmol potassium diet. Thirty-eight of the patients were taking digoxin and all were taking diuretics (37 patients frusemide alone, and five patients frusemide and spironolactone). All cardiac drugs except antiarrhythmic agents were withheld on the day of the study. Informed consent was obtained from each patient for the study procedure which had been approved by the University Committee on the Use of Human Subjects in Research.

On the morning of the study the patients fasted. In 36 patients a thermodilution Swan-Ganz flow-directed balloon tipped catheter was inserted percutaneously from a vein in the antecubital fossa and advanced to a position in the pulmonary artery where inflating the balloon occluded a pulmonary artery branch. The brachial artery was percutaneously cannulated with an Amplatz 0·038 arterial catheter. Pressures were monitored with Bell and Howell 4-3271 transducers. Electrocardiographic monitoring was continuous throughout the study. Pressure and electrocardiogram were recorded on a Hewlett Packard multichannel direct writing recorder. Mean pressures were electronically integrated. Right atrial pressure, pulmonary artery pressure, pulmonary capillary wedge pressure, and brachial artery pressure in mmHg, and thermodilution cardiac outputs in l/min were obtained. In the other six patients a venous line was passed from a vein in the antecubital fossa to obtain central venous pressure. Brachial artery pressure was measured by cuff sphygmomanometry and cardiac outputs were determined by the CO_2 rebreathing method using a Beckman LB2 gas analyser.[17]

After all catheters were positioned the subjects were allowed to rest for one hour. Haemodynamic measurements were then made and blood samples drawn for serum electrolytes, serum creatinine, and plasma renin activity by radioimmunoassay using a Renak assay (Roche) as described by Sealey *et al.*[18] The day before the study a 24-hour urine sample was collected for determination of sodium and creatinine excretion.

Systemic vascular resistance was calculated using the formula:

$$\text{SVR (dyne s cm}^{-5}\text{)} = \frac{\text{AP—RA}}{\text{CO}} \times 80,$$

where SVR is systemic vascular resistance, AP is brachial artery pressure, RA is right atrial pressure, and CO is cardiac output. Pulmonary vascular resistance was calculated using the formula:

$$\text{PVR (dyne s cm}^{-5}\text{)} = \frac{\text{PA}}{\text{CO}} \times 80,$$

where PVR is pulmonary vascular resistance, and PA is pulmonary artery pressure.

These data were analysed using variable linear regression and Student's t test.

Results

Resting haemodynamic, renal functional, and electrolyte data for the 42 patients studied are presented in Table 1. The low cardiac index and high right atrial and pulmonary capillary wedge pressures reflect the severity of the heart failure. Renal function was modestly diminished as evidenced by the slightly increased blood urea nitrogen and creatinine.

The plasma renin activity ranged from 0·3 ng/ml per h to 85·2 ng/ml per h (Fig. 1). The normal plasma renin activity in our laboratory ranges from 0 to 8·0 ng/ml per h. When the level of plasma renin activity was compared with the various aspects of haemodynamics, renal function, or electrolyte status, a strong ($p<0{\cdot}001$) inverse correlation ($r=-0{\cdot}65$) between plasma renin activity and serum Na^+ was found. No significant correlation was found between plasma renin activity and cardiac index, mean arterial pressure, pulmonary capillary wedge pressure, systemic vascular resistance, pulmonary vascular resistance, serum K^+, serum creatinine, or blood urea nitrogen (Table 1).

The patients were divided arbitrarily into a low renin group (0 to 16 ng/ml per h) and a high renin group (>16 ng/ml per h). There were 31 patients in the low renin group and 11 in the high renin group (Table 2). Serum Na^+ for the low renin group

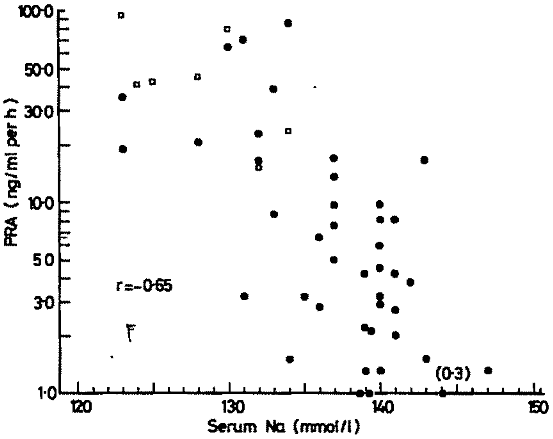

Fig. 1 *Correlation between plasma renin activity (PRA) and serum Na in patients with congestive heart failure. The closed dots represent the 42 patients studied. The open squares represent the seven patients prospectively marked as having high plasma renin activity because they were at the time hyponatraemic.*

Table 1 *Haemodynamic and renal function in patients with heart failure and their correlation to plasma renin activity*

	No.	*Mean*	*Correlation (r)*	*p for correlation*
CI (l/min per m²)	42	2·1 ± 0·1	0·15	NS
MAP (mmHg)	42	86·0 ± 2·0	−0·15	NS
PCW (mmHg)	35	24·4 ± 1·2	0·13	NS
RA (mmHg)	42	8·2 ± 0·9	−0·03	NS
SVR (dyne s cm⁻⁵)	41	1821 ±108	−0·07	NS
PVR (dyne s cm⁻⁵)	35	766 ± 58	0·12	NS
Urine Na+ (mmol/24 h)	27	51·1 ± 7·4	−0·05	NS
Serum creatinine (mmol/l)	41	114·9 ± 8·8	−0·06	NS
BUN (mmol/l)	40	9·99 ± 1·07	0·08	NS
Serum K+ (mmol/l)	41	4·1 ± 0·1	0·23	NS
Serum Na+ (mmol/l)	49	137 ± 1	−0·65	0·001

CI, cardiac index; MAP, mean arterial pressure; PCW, pulmonary capillary wedge pressure; RA, right atrial pressure; SVR, systemic vascular resistance; PVR, pulmonary vascular resistance; BUN, blood urea nitrogen.

Table 2 *Haemodynamics and renal function in high renin heart failure vs low renin heart failure*

	Low renin (31) *(0-16 ng/ml per h)*	*High renin (11)* *(>16 ng/ml per h)*	*Probability* *(low vs high)*
CI (l/min per m²)	2·1 ± 0·1	2·2± 0·2	NS
MAP (mmHg)	87·1 ± 2·1	83·0± 2·9	NS
PCW (mmHg)	24·4 ± 1·2	25·0± 1·3	NS
RA (mmHg)	7·9 ± 1·1	9·0± 2·1	NS
SVR (dyne s cm^{-5})	1876 ±122	1675 ±233	NS
PVR (dyne s cm^{-5})	747 ± 73	815 ± 99	NS
Urine Na$^+$ (mmol/24 h)	49·5 ± 6·5	57·8± 30·1	NS
Serum creatinine (mmol/l)	114·9 ± 8·8	1·3± 0·1	NS
BUN (mmol/l)	9·28± 1·07	33 ± 4	NS
Serum K$^+$ (mmol/l)	4·1 ± 0·1	4·5± 0·1	0·05
Serum Na$^+$ (mmol/l)	139 ± 1	131 ± 2	0·001

averaged 139±1 mmol/l vs 131±2 mmol/l for the high renin group. This difference was highly significant ($p<0·001$). Serum K$^+$ was also found to be significantly different ($p<0·05$) when the low renin group (K=4·1±0·1 mmol/l) was compared with the high renin group (K=4·5±0·1 mmol/l). In all other respects the groups were comparable. The degree of heart failure as measured by cardiac index, right atrial pressure, pulmonary capillary wedge pressure, systemic vascular resistance, or pulmonary vascular resistance was the same for both the high renin and low renin groups. Renal function as assessed by serum creatinine, blood urea nitrogen, and urinary Na$^+$ excretion was also similar for both groups.

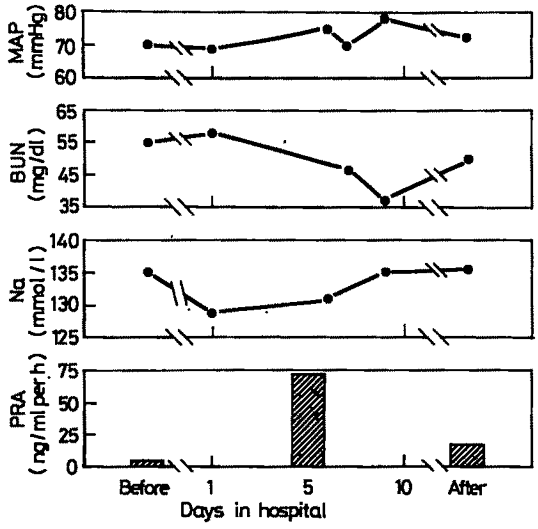

Fig. 2 *Changes in plasma renin activity (PRA), serum Na, blood urea nitrogen (BUN), and mean arterial pressure (MAP) with time in a patient with congestive heart failure. Plasma renin activity rose conspicuously at a time when the patient was hyponatraemic. Renal function did not deteriorate during this period as the blood urea nitrogen tended to fall. The high renin state was not accompanied by a rise in arterial pressure. To convert BUN figures to SI units, 1 mg/dl ≈ 0·357 mmol/l.*

Since analysis of these data suggested that hyponatraemia might identify high renin patients, a prospective analysis was undertaken by screening all patients admitted to hospital at the University of Minnesota Hospital during a two-month period because of congestive heart failure. Seven of these screened patients were found to be hyponatraemic (serum Na$^+$ 123-132 mmol/l). These patients were prospectively identified as having high renin heart failure. Subsequent plasma renin activity confirmed this in each patient: plasma renin activity ranged from 15·0 to 96·0 ng/ml per h (Fig. 1).

The dynamic relation between plasma renin activity and serum Na$^+$ was shown in one patient whose clinical course is shown in Fig. 2. This patient with severe congestive heart failure was admitted to hospital for a viral pneumonia. Before being admitted his serum Na$^+$ was normal and his plasma renin activity was low (3·2 ng/ml per h). During the acute illness he was found to be hyponatraemic. Plasma renin activity during that period was 71·2 ng/ml per h. With recovery, serum Na$^+$ levels returned to normal and plasma renin activity fell to (14·8 ng/ml per h). Mean arterial pressure was unchanged during this period despite activation of the renin angiotensin system. The rise in plasma renin activity could not be accounted for on the basis of decreased renal function, since the blood urea nitrogen tended to fall during the high renin period.

Discussion

The inverse correlation between plasma renin activity and serum Na$^+$ noted in this series of patients with congestive heart failure proved diagnostically useful. As shown in Fig. 3, hyponatraemia appears to be a marker for high renin heart failure, since plasma renin activity in the hyponatraemic group (mean 38·5±6·6 ng/ml per h) was significantly higher ($p<0·001$) than plasma renin activity in those with normal serum sodium (mean 5·1±0·8 ng/ml per h). Furthermore, in our prospective analysis all seven patients identified

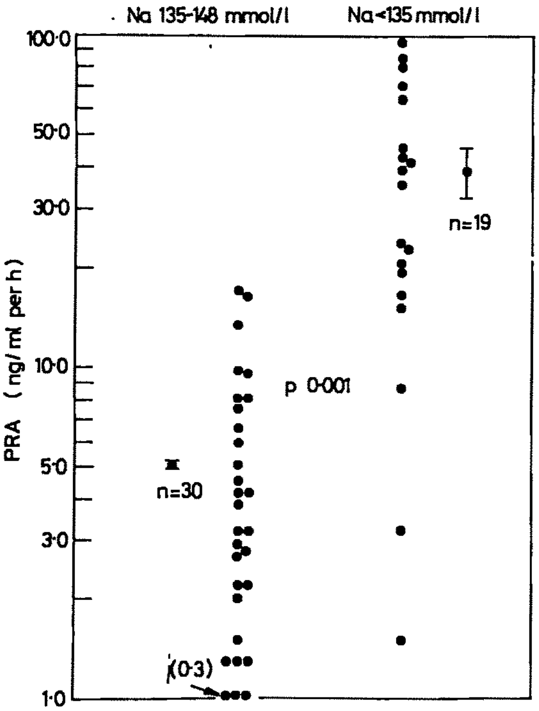

Fig. 3 *Plasma renin activity (PRA) in patients with normal serum sodium (Na) and in hyponatraemic patients. Plasma renin activity was significantly higher in the hyponatraemic group.*

with hyponatraemia had plasma renin activities greater than 15 ng/ml per h.

An inverse correlation between plasma renin activity and serum Na^+ in heart failure has been known for some time. Brown and associates[8] showed a very close inverse correlation in 17 untreated patients with heart failure. This strong inverse correlation was still present when 119 patients treated with diuretics and digitalis were analysed with the untreated patients. Hesse and co-workers[19] showed a significant rise in plasma renin activity as serum sodium fell in 12 patients with heart failure. The present study confirms these observations. Furthermore, in these treated patients with moderate to severe congestive heart failure, neither severity of heart failure as measured by cardiac index, pulmonary capillary wedge pressure, or right atrial pressure nor degree of renal impairment as measured by blood urea nitrogen or creatinine played an important role in determining plasma renin activity.

A number of pathophysiological mechanisms could be responsible for this inverse correlation between plasma renin activity and serum Na^+. Activation of the renin-angiotensin system results in increased levels of angiotensin II. The role of angiotensin II on renal absorption of Na^+ and water has been studied by a number of investigators,[8,20,21] who have suggested an angiotensin-mediated reduction in renal medullary blood flow. The resultant increase in medullary osmolarity could result in excessive water reabsorption. Angiotensin II by stimulating arginine vasopressin production could also contribute to increased water reabsorption[22,23] and hyponatraemia. We have recently shown raised arginine vasopressin levels in heart failure.[24] Finally, angiotensin II has been shown experimentally to stimulate the thirst centre and result in polydypsia.[25,26] The resultant hyponatraemia from any one or all of the above mechanisms could then directly stimulate renin secretion by a mechanism that is not entirely clear.[27,28] It is of interest that an inverse correlation between plasma renin and plasma sodium has been reported in hypertension.[29] Low serum sodium also is seen in the hyponatraemic hypertensive syndrome.[30] It is reasonable to assume that the same physiological mechanisms may be acting in the pathogenesis of hyponatraemia-hyper-reninaemia in all these situations.

Although plasma volume was not measured in these patients, the similar increases in right atrial pressure in the high and low renin groups and similar values for arterial pressure and cardiac output make it unlikely that differential stimulation of an intravascular volume receptor accounts for the high renin subgroup.

Although no correlation between plasma renin activity and serum K^+ was found, the potassium was significantly higher in the high renin than in the low renin group (Table 2). This trend is surprising, since high renin might be expected to induce secondary hyperaldosteronism[31] and potassium infusion decreases renal renin secretion.[32,33] Furthermore, this difference in serum K^+ could not be accounted for by differing diuretic regimens. The values for serum K^+ for both groups, however, were well within normal limits and the serum K^+ therefore was not useful in predicting the plasma renin activity.

The emergence of drugs that interfere with the renin-angiotensin system has made identifying those patients with high renin states potentially of clinical importance. Congestive heart failure has been treated with saralasin, a drug that competitively inhibits angiotensin II[9] and with converting enzyme inhibitors that block the formation of angiotensin II.[2,15,16,34,35] The acute response to these drugs appears to be closely correlated with the baseline plasma renin activity.[2,35,36] Table 3 shows the effectiveness of acute converting enzyme inhibition in four selected hyponatraemic patients with high renin heart failure. Mean arterial pressure and pulmonary capillary wedge pressure were significantly lowered and cardiac index significantly increased. Though preliminary

Table 3 *Response of patients with high renin heart failure to one dose of captopril, an angiotensin converting enzyme inhibitor*

Case No.		*Na⁺ (mmol/l)*	*PRA (ng/ml per h)*	*MAP (mmHg)*	*PCW (mmHg)*	*CI (l/min per m²)*	*SVR (dyne s cm⁻⁵)*
1	B	132	70·0	75	26	2·2	1455
	C			50	8	2·6	836
2	B	131	63·8	100	38	1·6	3409
	C			45	9	2·4	1166
3	B	132	22·8	92	22	1·2	3163
	C			60	9	1·6	1640
4	B	134	85·2	78	25	3·2	888
	C			56	8	3·5	556
Mean±SD	B			86±5	27·8±3·2	2·1±0·4	2229±557
	C			53±3*	8·5±0·31*	2·5±0·3*	1050±208

B, baseline; C, after captopril.
*$p<0·05$.

reports suggest that converting enzyme inhibitors may have beneficial long-term effects even in low renin heart failure,[36] their mechanism of action in this setting is not entirely understood. Identification of high renin heart failure might be useful in selecting appropriate acute therapy. The present data suggest that a low serum sodium is a simple indicator of such cases and might identify patients who will acutely benefit most from therapy to inhibit the renin-angiotensin system.

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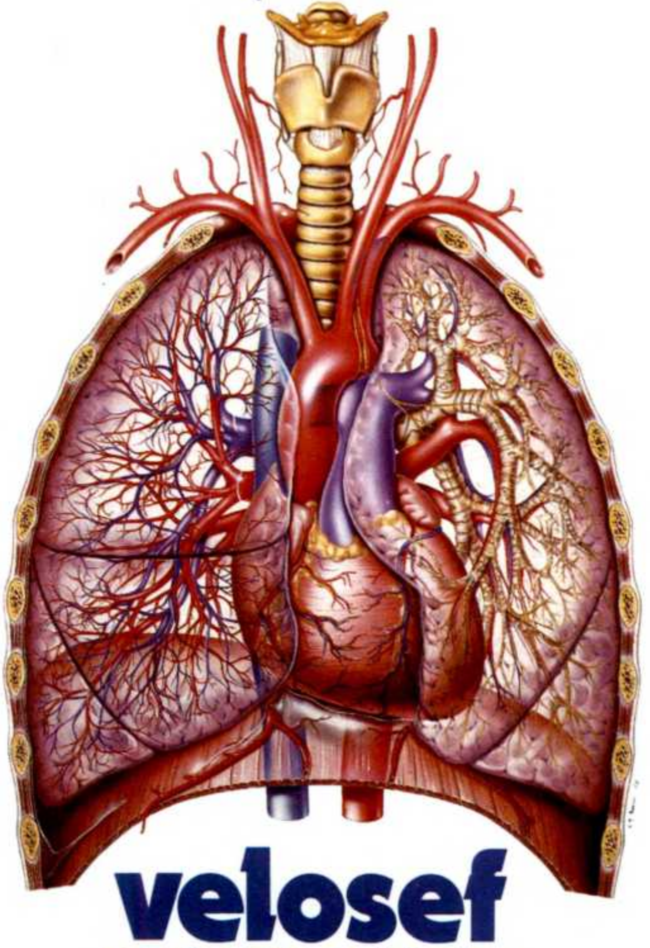

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Extent of myocardial damage after open-heart surgery assessed from serial plasma enzyme levels in either of two periods (1975 and 1980)

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SUMMARY Perioperative myocardial damage caused by cardiac surgery in 32 patients operated upon in 1980 is quantified in terms of total quantity of alpha-hydroxybutyrate dehydrogenase released from the heart into the circulation, and compared with perioperative myocardial damage in 32 patients operated upon in 1975. In the five year period between 1975 and 1980, various aspects concerning anaesthesia, pharmacological treatment, and myocardial preservation techniques have been subjected to considerable changes. Comparison of calculated myocardial damage in 1980 with that in 1975 shows a general reduction of about 40% in patients having coronary artery bypass grafting, 75% in patients with aortic valve replacement, and 10% in patients with mitral valve replacement.

In an earlier report[1] we described the extent of myocardial damage in 15 patients after coronary artery bypass grafting, in 10 patients after aortic valve replacement, and in seven patients after mitral valve replacement. Cardiac damage was assessed by the enzymatic method in which the activity of an enzyme that has been released by the heart into the circulation is computed. The patients described in the earlier report underwent cardiac surgery in 1975.

Since then, anaesthetic and surgical techniques and procedures have improved considerably. For instance, the introduction of new cardiac preservation techniques, such as hypothermic potassium-induced cardioplegia, has generally proved to be of great value.[2-4] Therefore, the above-mentioned study was repeated in 1980 using the same number of patients in the three surgical groups and the same method to assess myocardial damage.

Subjects and methods

This study comprised two groups each of 32 patients operated upon in 1975 and 1980, respectively. Three subgroups were distinguished in each group: 15 patients having coronary artery bypass grafting, and 10 and seven patients having replacement of aortic and mitral valve, respectively. Table 1 shows the clinical data.

Surgical techniques with respect to the patients operated upon in 1975 were previously described.[1] In 1975 and in 1980 cardiac surgery was performed with standard cardiopulmonary bypass techniques. In both years mild systemic hypothermia, haemodilution, and topical myocardial cooling with iced saline were employed. While in 1975 patients had anoxic cardiac arrest (coronary artery bypass grafting group) or coronary perfusion with hypothermic blood (aortic and mitral valve replacement groups) all patients operated upon in 1980 had hypothermic potassium-induced cardioplegia using St. Thomas's Hospital cardioplegic solution,[5] infused at a pressure of about 40 mmHg and repeated every half an hour.

Table 1 shows the duration of cardiopulmonary bypass and aortic cross-clamping as well as minimal body temperature. A standard 12 lead electrocardiogram was recorded before operation and repeated at least once daily after operation. The only electrocardiographic criterion used to assess perioperative myocardial infarction was the appearance of new or deeper Q waves of at least 0·04 s duration.[6 7]

ENZYME ASSAYS

Venous blood samples were obtained before, just before the start of cardiopulmonary bypass (time

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zero), immediately after termination of cardiopulmonary bypass, and subsequently every six hours for 36 hours. Blood was drawn on trisodium citrate and centrifuged twice at 1174 x *g* for 10 minutes. The plasma activity of alpha-hydroxybutyrate dehydrogenase was assayed with alpha-keto-butyrate as a substrate[8] using a test kit (Boehringer, 124818). Alpha-hydroxybutyrate dehydrogenase activity represents the activity of the H subunits of lactate dehydrogenase (LDH, EC 1.1.1.27), and is expressed in units per litre plasma, in which 1 unit of alpha-hydroxybutyrate dehydrogenase catalyses the conversion of 1 μmol substrate per minute at 25°C.

MATHEMATICAL CALCULATION OF MYOCARDIAL DAMAGE BASED ON PLASMA ALPHA-HYDROXYBUTYRATE DEHYDROGENASE (HBDH)

The quantity of enzyme released per litre of plasma during the first 36 hours after operation, denoted as A_{HBDH} (36), is taken as a measure of perioperative myocardial damage. As discussed by Norris *et al.*,[9] this quantity should be preferred as a clinical index to the quantity of enzyme expressed in grams of destroyed tissue. For purposes of quantification the plasma HBDH activity was determined at various times after onset of injury. It can be assumed from the low plasma levels of HBDH seen immediately after operation that no significant haemolysis occurs during operation. The calculation and the mathematical model used are described in a previous paper[1] and in more detail elsewhere.[10] The variable values of the two-compartment model used have recently been estimated with greater precision by Willems *et al.*[11] A fixed mean value of 0·015 h^{-1} was used for the clearance constant of HBDH.[11] As the 32 patients operated upon in 1975 were analysed earlier with slightly different variable values, calculation of individual values of A_{HBDH} (36) was repeated for these patients. A more common procedure on quantification of myocardial injury followed by many investigators uses creatine kinase (CK) or CK MB.[12-14] When applying a fixed rate for the enzyme's clearance constant k, it appears that a considerable interindividual variation in the value of k produces only small variations in the calculated total quantity of an enzyme released, provided the enzyme is cleared from the circulation slowly.[15] This important condition is fulfilled by choosing HBDH. The fast disappearance kinetics of CK and CK MB, as calculated by Willems *et al.*,[11] make them less appropriate for purposes of quantitative assessment of the extent of myocardial damage.

STATISTICAL METHODS

Statistical significance of differences between means of two groups of values was calculated using Student's t test when samples proved to have a normal distribution. When values were not distributed normally, median values ± 95% confidence limits were given, and for testing differences between two groups of values the Wilcoxon rank test was employed. Linear regression analysis was employed to detect whether a linear correlation existed between pairs of values of two normally distributed variables. When variables were not distributed normally Spearman's rank test was used to disclose a rank correlation. For analysis of statistical significance between two groups of data on the incidence of a *yes-or-no* phenomenon (for example mortality) the χ^2-test has been used.

Results

The Fig. shows the median values ± 95% confidence limits of calculated total quantity of HBDH released (A_{HBDH}) as a function of time for the six groups of patients dealt with in this study. In fact, these curves represent the time-dependent release of HBDH activity into the plasma corrected for (1) preoperative plasma HBDH values, (2) clearance of HBDH activity from the plasma, and (3) extravasation of HBDH activity. The six curves depicted in the Fig. show that at 24 hours after the start of extracorporeal circulation ($t=0$) HBDH release from the injured heart into the circulation has almost come to a stop. As the aortic valve replacement group of 1975 still shows some progression of HBDH release in the next 12 hours, the A_{HBDH} values as calculated 36 hours after the start of extracorporeal circulation have been taken to represent the ultimate myocardial damage resulting from cardiac surgery.

Comparison of the results of 1980 with those of 1975 discloses a significant ($p<0{\cdot}05$) reduction in myocardial damage in the coronary artery bypass graft group of about 40%, and a highly significant ($p<0{\cdot}01$) reduction in the aortic valve replacement group of about 75%.

The greater degree of damage in 1975 compared with 1980 in the coronary artery bypass graft group corresponds to a higher incidence of new Q waves in the electrocardiogram and a higher mortality in the first postoperative week in the patients operated on in 1975 when compared with those operated on in 1980 (see Table 1).

When we correlate enzymatic heart damage with duration of extracorporeal circulation in patients operated on in 1975 and 1980 no correlation was found (correlation coefficients of 0.28 and −0·07, respectively) using Spearman's rank test. When A_{HBDH} (36) is correlated with duration of aortic occlusion the correlation coefficients are −0·15 and 0·09, respectively, using the same test.

Although the period of aortic occlusion was longer in 1980 than in 1975 by a factor of 1·6 (see Table 1) cardiac surgery produced less cardiac damage in 1980 than in 1975. In the coronary artery bypass graft group the longer duration of aortic occlusion in 1980 compared with 1975 can be ascribed to grafting of more distal anastomoses (3·1 vs. 1·9; p<0·01) on the coronary artery system in 1980. In the aortic valve replacement group the reduction of myocardial damage in 1980 compared with 1975 is associated with a shortening of the duration of extracorporeal circulation (92 vs. 156 minutes; p<0·01).

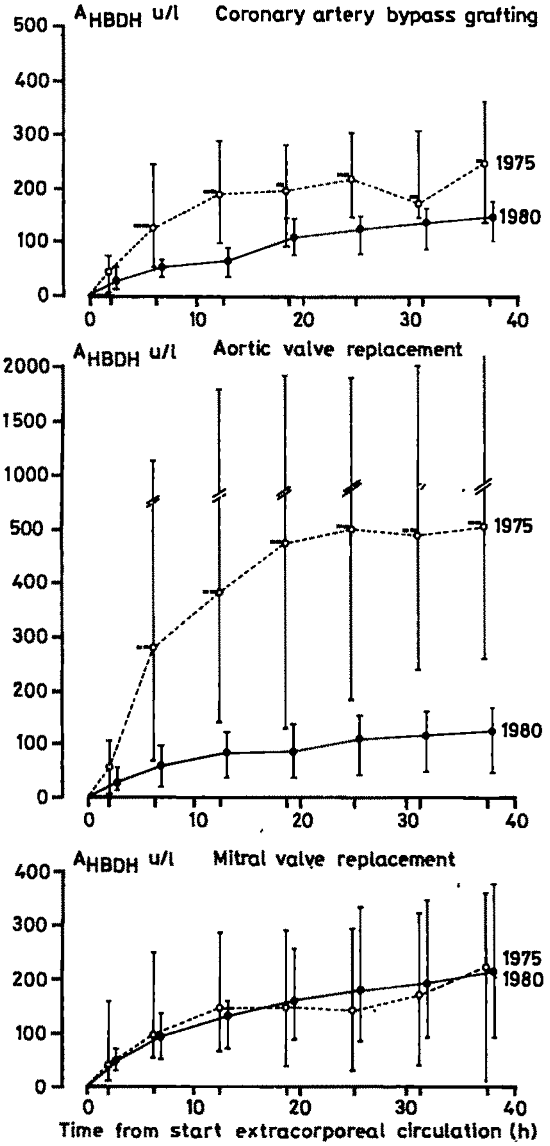

Fig. *Time course of the calculated quantity of alpha-hydroxybutyrate dehydrogenase (HBDH) released per litre plasma (A_{HBDH} u/l) in the patients operated upon in 1975 (○) and 1980 (●) for coronary artery bypass grafting (n=15 in each year), aortic valve replacement (n=10 in each year), and mitral valve replacement (n=7 in each year). Indicated are medians ± 95% confidence limits. Differences between 1975 and 1980 are tested with a two-tailed Wilcoxon rank test: *$p<0{\cdot}05$ and **$p<0{\cdot}01$.*

Although an increase in the number of bypassed obstructions in the coronary artery bypass graft group and a decrease in duration of extracorporeal circulation in the aortic valve replacement group will be of benefit to the surgically treated patients the pronounced difference in perioperative myocardial damage as found in 1975 and 1980 is, most probably, to be ascribed to other factors as well. Also to be excluded are age and preoperative exercise tolerance of patients as well as the indications for cardiac surgery and body temperature during extracorporeal circulation (see Table 1) since they were not essentially different in 1980 when compared with 1975. Factors which are considered as likely to be responsible for the reduction of myocardial damage in patients operated on in 1980 compared with those operated on in 1975 are: the anaesthetic procedure, the pharmacological treatment, topical cooling of the heart, and use of cardioplegia instead of (intermittent) coronary perfusion.

ANAESTHESIA

Several changes in the anaesthetic regimen have been implemented between 1975 and 1980. Table 2 provides information about the anaesthetic procedures employed.

The improvement in the whole anaesthetic regimen is aimed at avoiding large variations in blood pressure and heart rate to permit an optimal balance between myocardial oxygen supply and demand.

PHARMACOLOGICAL THERAPY AND CIRCULATORY SUPPORT

Pharmacological treatment before, during, and after cardiac surgery has changed in several respects between 1975 and 1980. In 1975 all patients in the coronary artery bypass graft group who were on beta-receptor blocking drugs (14/15) stopped this treatment two to three days before operation. In the years after 1975, patients of the coronary artery bypass graft group who used beta-receptor blocking drugs continued to use these drugs till the very day of cardiac surgery. It is believed that the oxygen-sparing effects of beta-blocking agents in patients with severe coronary artery lesions is beneficial particularly during cardiac surgery. Table 3 shows the number of patients receiving respiratory support, cardiac pacemaker, intra-aortic counterpulsation, and certain drugs acting on heart and circulation, such as beta-adrenergic agonists, digitalis, vasodilators, calcium antagonists, and beta-adrenergic blocking agents.

Table 1 *Three groups of patients operated upon in 1975 compared with three groups of patients operated upon in 1980: coronary artery bypass grafting, aortic valve replacement, and mitral valve replacement*

	Coronary artery bypass graft				*Aortic valve replacement*				*Mitral valve replacement*		
	1975	*1980*	*p*†		*1975*	*1980*	*p*†		*1975*	*1980*	*p*†
No. of patients	15	15			10	10			7	7	
Sex Male	12	13			8	7			2	0	
Sex Female	3	2			2	3			5	7	
Age Mean (y)	50·5	57·4			46·5	52			58	51·2	
Age Range (y)	35–62	37–69			22–69	18–66			46–68	21–70	
Preoperative exercise tolerance* II	1	2			4	4			0	0	
III	13	12			6	5			5	5	
IV	1	1			0	1			2	2	
Valvular abnormality¶				AS	2	2		MS	1	4	
				AR	3	5		MR	3	2	
				AS+AR	5	3		MS+MR	3	1	
No. of distal anastomoses‡	1·9±0·7	3·1±1·1	<0·01								
Range	1–3	1–5									
Period of extra-corporeal circulation‡ (min)	118±50	127±38	NS		156±67	92±15	<0·01		120·0±38·0	89±22	NS
Period of aortic cross clamping‡ (min)	34±16	61±22	<0·01		48±38	62±14	NS		36·0±8·0	58±16	<0·05
Minimal body temperature‡ (°C)	28·2±3·2	27·1±1·2	NS		28·3±1·6	28·3±0·3	NS		25·1±3·4	28±0·6	<0·05
New Q waves in electrocardiogram§	4/15	0/15			2/10	0/10			0/7	0/7	
Mortality in first postoperative week	2/15	0/15			1/10	0/10			0/7	0/7	

*Classification according to the New York Heart Association.
†Using the two-tailed Student's t test.
‡Mean value ± SD.
§Indicative of perioperative infarction.
¶AS: aortic stenosis; AR, aortic regurgitation; MS, mitral stenosis; MR, mitral regurgitation.

Table 2 *Data concerning anaesthesia of two groups of patients operated on in 1975 and 1980*

Drugs administered	*1975 CABG*	*AVR*	*MVR*	*All patients*	*1980 CABG*	*AVR*	*MVR*	*All patients*	*Relative change in 1980 compared with 1975*
Premedication									
Opiates	15/15	10/10	7/7	32/32	8/15	8/10	4/7	20/32	↓
Atropine	14/14†	10/10	7/7	31/31†	8/15	3/10	4/7	15/32	↓
Lorazepam	0/15	0/10	0/7	0/32	15/15	9/10	7/7	31/32	↑↑
Induction of anaesthesia									
Thiopentone	14/15	10/10	7/7	31/32	9/15	8/10	3/7	20/32	↓
Nicomorphine	0/15	0/10	1/7	1/32	6/15	5/10	3/7	14/32	↑↑
Muscle relaxant*	15/15	10/10	7/7	32/32	15/15	10/10	7/7	32/32	—
Calcium chloride	14/15	9/10	7/7	30/32	6/15	2/10	0/7	8/32	↓↓
Fentanyl	0/15	0/10	0/7	0/32	12/15	7/10	5/7	24/32	↑↑
Maintenance of anaesthesia									
100% O_2	15/15	10/10	7/7	32/32	7/15	4/7†	2/6†	13/28†	↓
O_2/N_2O	0/15	0/10	0/7	0/32	8/15	5/8†	3/5†	16/28†	↑↑
Halothane	15/15	7/10	5/7	27/32	0/15	0/10	0/7	0/32	↓↓
Enflurane	0/15	3/10	2/7	5/32	6/15	5/10	37	14/32	↑
Nicomorphine	15/15	10/10	7/7	32/32	4/15	2/10	2/7	8/32	↓↓
Fentanyl	0/15	0/10	0/7	0/32	13/15	10/10	7/7	30/32	↑↑

*For example, pancuronium bromide and succinyl choline.
†Complete data not available.
CABG, coronary artery bypass graft; AVR, aortic valve replacement; MVR, mitral valve replacement.

From 1975 to 1980 one can distinguish a shift in the use of positive inotropic interventions to interventions that lead to decreased peripheral resistance and negative-inotropic responses.

TOPICAL COOLING OF HEART

A number of patients received topical cooling of the heart with ice-cold saline during operation, either once or continuously by means of Topical Cooling Device (Cobe). Statistical analysis using the χ^2 test reveals that topical cooling of the heart was applied more often in 1980 than in 1975 in the coronary artery bypass graft group (15/15, instead of 10/15; $p<0·05$), aortic valve replacement group (10/10, instead of 4/10;

$p<0{\cdot}01$), and mitral valve replacement group (5/7, instead of 1/7; $p<0{\cdot}05$).

MYOCARDIAL PRESERVATION TECHNIQUE

In all 32 patients operated on in 1980 cardiac arrest during open-heart surgery was induced and maintained by hypothermic potassium-induced cardioplegia. In 1975 patients from the coronary artery bypass graft group had intermittent coronary perfusion with hypothermic blood. In 1975 patients from the aortic valve replacement group had continuous coronary perfusion with hypothermic blood by selective cannulation of the coronary ostia. This method has a number of disadvantages: narrow or calcified ostia of the coronary artery are often the cause of improperly fitting perfusion cannulae. In addition, proximal side branches of the coronary artery system can easily be obstructed by the inserted perfusion cannulae. In 1975 patients from the mitral valve replacement group had continuous coronary perfusion with hypothermic blood via a needle inserted in the aorta proximally of the cross-clamp.

Discussion

The results presented in this study demonstrate that in a five year interval (1975 to 1980) cardiac injury after coronary artery bypass grafting and aortic valve replacement had decreased considerably. This finding was previously reported by Kouchoukos *et al.*[16] who compared mortality from coronary artery bypass grafting in the period 1970 to 1973 with that in the period 1974 to 1977. They reported that 30 day mortality as well as incidence of definite or probable perioperative myocardial infarction in the two periods fell from 2·7% to 1·2% ($p<0{\cdot}01$) and 11·4% to 2·4% ($p<0{\cdot}001$), respectively, despite the fact that in the period 1974 to 1977 more vessels were grafted (mean number 2·9) than in the period 1970 to 1973 (mean number 1·9). In the present study the decrease of the extent of perioperative myocardial injury was more pronounced in the group of patients having aortic valve replacement than in the group of patients with coronary artery bypass grafting. Earlier[1] we proposed that selective coronary artery perfusion of the hearts in which the aortic valve had to be replaced might have been inadequate in perfusing the subendocardial layers of the heart, because of the hypertrophied state of the hearts of the aortic valve replacement group. The tremendous decrease of perioperative myocardial injury in the aortic valve replacement group possibly means that development of extensive subendocardial ischaemia has been prevented. In this context the change of myocardial preservation technique to hypothermic, potassium-induced cardioplegia may be considered as the factor responsible for the significant improvement of perioperative cardiac damage. In the coronary artery bypass graft group several factors can be held responsible for the improvement of perioperative myocardial injury. Apart from a change in preservation technique, changes in medical treatment, such as continued administration of beta-blocking agents till the day of operation, as well as changes in anaesthetic regimen may have helped to optimise the balance between oxygen supply and energy requirements of the heart. Hypothermic, potassium-induced cardioplegia is not the only factor responsible for improvement of perioperative myocardial injury, for in the mitral valve replacement group no significant improvement in the interval 1975 to 1980 could be demonstrated. Though the mitral valve replacement groups contained only seven patients it was shown earlier[1] that in this group myocardial damage after surgery was small when compared with cardiac damage in the groups of patients undergoing coronary artery bypass grafts and aortic valve replacement. Therefore, we believe that in the mitral valve replacement group medical care, anaesthetic treatment, and surgical techniques were relatively optimal already, so that the improvements mentioned before did not result in a further decrease of perioperative myocardial damage.

Table 3 *Pharmacological treatment and circulatory support given perioperatively to two groups of patients operated on in 1975 and 1980*

Treatment	*1975*	*1980*	*Relative change in 1980 compared with 1975*
Respiratory support (postop.)	29/32	31/32	—
Pacemaker	7/32	9/32	—
Intra-aortic balloon pump	4/32	1/32	↓
Adrenaline/isoprenaline	24/32	0/32	↓↓
Dopamine/dobutamine	9/30*	9/32	—
Cardiac glycosides	18/32	29/32	↑
Vasodilators‡	0/32	11/32	↑↑
Antiarrhythmic drugs§	5/32	6/32	—
Nifedipine	0/32	2/32	↑
Beta-receptor blocking agents¶	2/32†	17/30*	↑↑

*Complete data not available.
†Patients from the coronary artery bypass grafting group treated with beta-receptor blocking agents preoperatively (14/15) did not receive these drugs in the last two to three days before operation.
‡For example, nitroprusside and glyceryl trinitrate.
§For example, lignocaine and disopyramide.
¶For example, propranolol, atenolol, metoprolol, and acebutolol.

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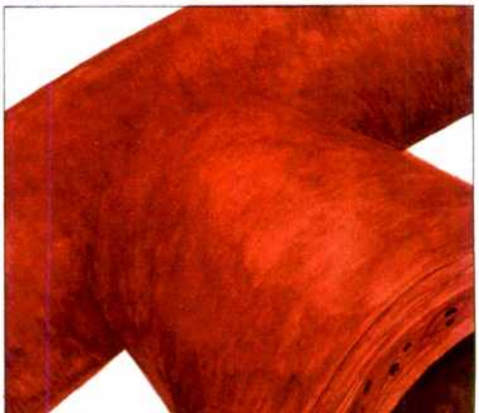

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Br Heart J 1982; 47: 173–6

"Duplication" of aortic cusp
New M-mode echocardiographic sign of intimal tear in aortic dissection

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SUMMARY M-mode and two-dimensional echocardiograms were obtained in a patient with acute dissecting aneurysm of the ascending aorta. The M-mode echocardiogram disclosed apparent "duplication" of the non-coronary aortic cusp. Two-dimensional echocardiograms showed this finding to be the result of the motion of a flap of torn aortic intima. This new M-mode finding appears to be a highly specific echocardiographic sign for aortic dissection.

M-mode echocardiographic techniques have proved useful in the detection of dissecting aneurysm of the aorta in patients in whom the disorder is clinically suspected.[1–5] Their use is limited by an undetermined incidence of false negatives and false positives. We present a new M-mode finding of dissection—apparent "duplication" of an aortic valve cusp. A two dimensional echocardiographic study in this case shows that this finding was caused by the motion of a flap of torn aortic intima and suggests that this M-mode finding may be highly specific for aortic dissection.

Methods

M-mode and two dimensional echocardiograms were recorded using a Toshiba SSH-10A sonolayergraph. This is a phased array scanner which uses a 32 element transducer with a frequency of 2·4 MHz and a scanning angle of 78°. A single element can be selected and aimed during two dimensional viewing to record an M-mode recording of the area of interest.

M-mode recordings were made on a Honeywell 1896 strip chart recorder on dry silver paper. Two dimensional videotape recordings were made of the same area within minutes of the M-mode recording and stop frame photographed from a monitoring television screen.

Case report

A 35-year-old black man presented with a three week history of increasing dyspnoea on exertion, orthopnoea, paroxysmal nocturnal dyspnoea, ankle oedema, and palpitation. He had been known to have a heart murmur for 15 years. There was no history of chest pain. He had been seen as an outpatient one year and again two months before admission and had been noted to have a blood pressure of 270/150 mmHg in both arms, but he had refused admission or treatment. On physical examination he was in moderate respiratory distress. The blood pressure was 180/52 mmHg in both arms, the heart rate was 140, and the respiratory rate 40. The jugular venous pressure was normal and the carotid pulses were hyperdynamic. There were râles half way up the chest bilaterally. The apex beat was diffuse and laterally displaced. The first sound was loud, the second sound single, and there was a loud summation gallop. There was a grade 3/6 systolic ejection murmur heard all over the praecordium. There was a grade 3/6 blowing decrescendo diastolic murmur, loudest at the left sternal border and radiating to the apex. There was moderate bilateral ankle oedema. Certain features suggested Marfan's syndrome: a height of 198 cm (6 ft, 6 in), pectus excavatum, a high arched palate, arachnodactyly, and hyperextensible joints. The chest *x*-ray film showed cardiomegaly, dilatation of the ascending aorta, and pulmonary oedema. The electrocardiogram showed sinus tachycardia, left atrial "enlargement", borderline voltages for left ventricular hypertrophy, and nonspecific lateral ST-T changes. The patient was stabilised on nasal O_2, morphine, intravenous frusemide, and a nitroprusside infusion. Both

M-mode and two dimensional echocardiograms were obtained (see Results). An aortogram, performed during nitroprusside infusion, showed a type I dissecting aneurysm starting near the origin of the right coronary artery, and involving the right lateral wall of a massively dilated aortic root. There was free communication between the true and false lumens and gross aortic regurgitation. The central aortic pressure was 150/60 (mean 88 mmHg). Right heart pressures were normal. The mean pulmonary capillary wedge pressure was 18 mmHg. The mixed venous oxygen saturation was 45 per cent (haematocrit 45%). These findings were consistent with left ventricular failure and a low output state. At operation incision into the aorta disclosed a wide intimal tear of the ascending aorta beginning slightly superior to the right coronary ostium, and a large type I dissecting aneurysm extending up the right lateral wall of the arch. The proximal portion of the dissected intima lay on the aortic valve, and the distal portion formed a large false lumen. The aneurysm was repaired, the tricuspid aortic valve replaced, and a right coronary artery bypass graft performed. The patient recovered uneventfully after control of his hypertension. Pathological examination of the resected aortic leaflets showed myxomatous changes.

Results

The M-mode echocardiographic study disclosed a hyperdynamic, concentrically hypertrophied ventricle with a shortening fraction of 25 per cent and an ejection fraction[6] of 49 per cent. At the level of the aortic root the aortic diameter measured 4·3 cm (1·9 cm/m^2) and the left atrium measured 2·3 cm (1·0 cm/m^2). There was thickening of the right coronary valve cusp. Slight superior sweep of the transducer from this position showed further dilatation of the aorta to a dimension of 5·3 cm (2·3 cm/m^2) with compression of the left atrium to 1·6 cm (0·7 cm/m^2) (Fig. 1). Inspection of the aortic valve cusps at this level showed the presence of a structure (curved arrows) which lay posterior to the non-coronary cusp (straight arrows) and generally paralleled its motion. The onset of its end-systolic anterior motion was slightly delayed relative to the true cusp and it appeared to join both aortic cusps in diastole.

The genesis of this apparent "duplication" of the non-coronary cusp can be understood by inspection of the two dimensional long axis echocardiograms recorded within minutes of the M-mode tracings. Fig. 2 shows a systolic frame from a videotape of the dilated aortic root, left ventricle, and compressed left atrium. A line is superimposed on the sector scan to show the angle of incidence of a single M-mode beam which would produce the systolic M-mode image. The origin of this line does not pass through the apex of the sector scan because of slight alteration in transducer placement between M-mode and two dimensional recordings. The flap of torn intima (arrows) can be seen behind the non-coronary cusp extending cephalad in the dilated ascending aorta. Fig. 3 shows the same view in diastole with the flap of torn intima (arrows) now having prolapsed on to the closed aortic leaflets (thicker arrow), which would produce the M-mode appearance of conjunction of the "duplicated" leaflet with the true aortic leaflets.

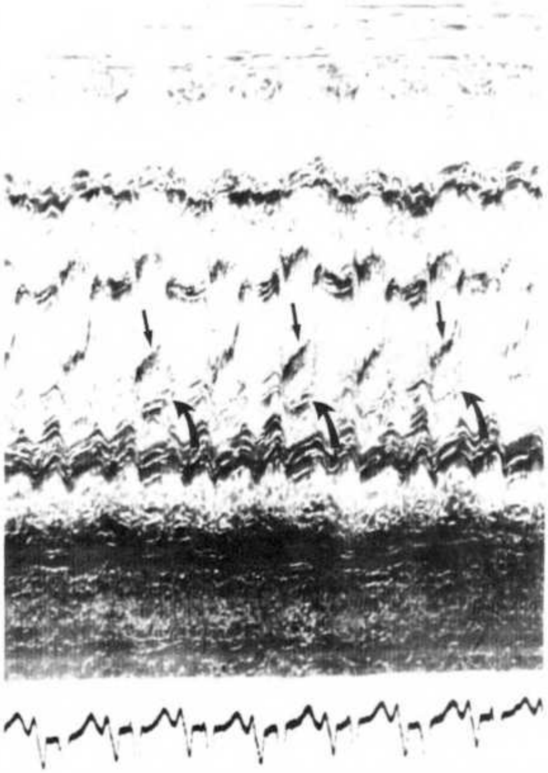

Fig. 1 *M-mode recordings of the aortic root. The curved arrows indicate the "duplication" of the non-coronary cusp. The straight arrows indicate the true non-coronary cusp. The "duplicated" cusp moves anteriorly to join the true cusps slightly after the true cusp closure. The aorta is dilated and the left atrium is compressed.*

Discussion

M-mode echocardiographic criteria for dissecting aneurysm of the ascending aorta as proposed by Nanda *et al.*[1] include: (1) dilatation of the aortic root (> 42 mm); (2) separation and widening of the anterior aortic wall (16 to 21 mm) and/or posterior

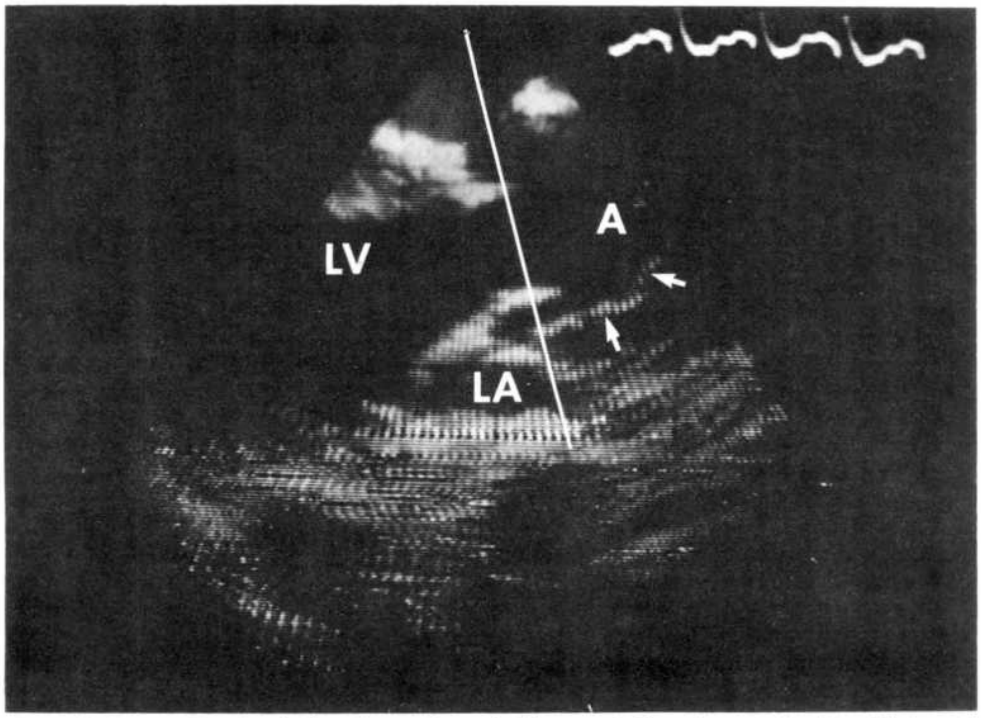

Fig. 2 *Long axis view two dimensional echocardiogram in systole. The arrows indicate the torn intimal flap. The long white line indictes a single M-mode beam which would produce the systolic M-mode image. LV, left ventricle; LA, left atrium; A, aortic lumen.*

aortic wall (10 to 13 mm); (3) parallel motion of the separated walls. All three criteria are required for the diagnosis. Fluttering of the anterior mitral leaflet (caused by aortic regurgitation) and pericardial effusion are supportive as signs of complications of dissection. Brown *et al.*[2] have emphasised that these criteria can lead to false positive diagnoses unless anterior aortic wall thickening is present *and* the patient is clinically suspected of having dissection. Conversely, false negative echo studies may result from asymmetric dissections[3] or dissections in the adventitial space surrounding the aorta.[4] Among commoner causes of a false positive diagnosis are dilatation of the ascending aorta[3] and non-specific thickening or calcification of the aortic root.[5]

De Maria *et al.*[7] have recently reported on the superiority of two-dimensional echocardiography to M-mode for the detection of aneurysm of the ascending aorta. Nevertheless, M-mode evidence of aortic enlargement was found in 11 of their 12 cases. Only one of their three patients with aortic dissection had M-mode findings consistent with this diagnosis. To our knowledge there is no information based on a large number of cases on the sensitivity of M-mode echocardiography in diagnosing this disorder. The case under discussion did not meet the second criterion of Nanda *et al.*[1]

M-mode echocardiography remains a useful, relatively inexpensive, and readily available technique in clinical cardiology. The apparent "duplication" of the non-coronary cusp detected by M-mode study, shown to be caused by the motion of a flap of torn intima by two-dimensional echocardiography, is a new finding in dissecting aneurysm of the ascending aorta. Though this finding appears to be highly specific for this diagnosis it is conceivable that a mobile vegetation or clot at the base of the aorta in proximity to an aortic leaflet might produce similar appearances. Such a finding, however, has never been reported to our knowledge. Diagnostic confusion is also unlikely because of clinical and other echocardiographic characteristics of such lesions. It is likely that similar "duplication" of the right coronary cusp may be produced by anterior dissection of the aorta. Thus we have identified a new M-mode echocardiographic finding in aortic dissection which is probably highly specific. Its sensitivity awaits further study.

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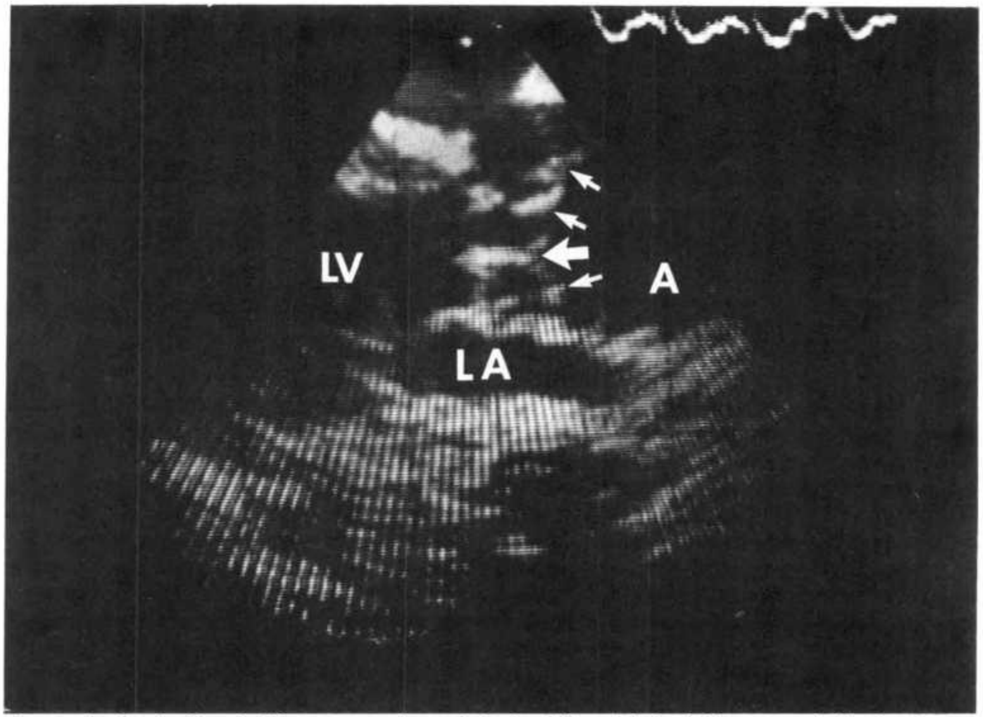

Fig. 3 *Long axis view in diastole. The arrows point to the intimal flap with the thicker arrow indicating its contact with the conjoined true leaflets. Abbreviations as in Fig 2.*

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Syncope in hypertrophic cardiomyopathy

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SUMMARY A patient with hypertrophic cardiomyopathy, syncope, and frequent ventricular tachycardia was monitored during a syncopal episode. An unrecordable blood pressure and the loss of a left ventricular outflow tract murmur without evidence of arrhythmia suggested a primary haemodynamic mechanism such as reduction in left ventricular volume.

Death is often sudden in hypertrophic cardiomyopathy[1] and is associated with syncope[2] and serious ventricular arrhythmia.[3] Though asystole,[4] complete heart block,[5] rapid atrioventricular conduction precipitating ventricular fibrillation,[6] and massive myocardial infarction[7] have been documented, the cause of death remains uncertain in the majority of patients who die suddenly. Acute haemodynamic deterioration with increased left ventricular outflow tract gradient or tachycardia with decreased stroke volume have been proposed but never documented as the antecedent mechanism.[8] We present a patient with hypertrophic cardiomyopathy, syncope, and frequent ventricular tachycardia, who was monitored during a syncopal episode, with loss of blood pressure and left ventricular outflow tract murmur without ventricular tachycardia.

Case report

A 52-year-old nursing sister was well until 1978 when she began to experience palpitation. She was found to have a jerky, ill sustained pulse, a palpable left atrial beat with prominent left ventricular impulse, and a mid-systolic murmur. The electrocardiogram showed left ventricular hypertrophy with repolarisation changes, the chest radiograph was normal, and M-mode echocardiogram disclosed a thickened ventricular septum (2·2 cm) with mid-systolic closure of the aortic valve and systolic anterior motion of the mitral valve. The diagnosis of hypertrophic cardiomyopathy was made and propranolol 40 mg daily was started. The patient continued to experience palpitation and developed increasing breathlessness and chest heaviness during effort. On Boxing Day 1979, she had a prolonged syncopal episode. This was preceded by the sudden onset of fast palpitation after rising from a chair. Subsequently ambulatory electrocardiographic monitoring disclosed frequent short episodes of ventricular tachycardia. The propranolol was increased to 120 mg per day, but she experienced another syncopal episode. This was preceded by tachycardia which persisted after climbing stairs quickly. Mexilitene 600 mg daily was added and the patient was referred to the Hammersmith Hospital.

While she was on mexilitene and propranolol the patient continued to have daily episodes of ventricular tachycardia (Fig. 1). Propranolol and mexilitene were stopped. Treadmill exercise tests were performed and the patient exercised for six minutes, completing stage 2 of the Bruce protocol.[9] Cardiac catheterisation and left ventricular angiography confirmed the diagnosis of hypertrophic cardiomyopathy. Left ventricular end-diastolic pressure was 16 mmHg, and there was a resting left ventricular outflow tract gradient of 50 mmHg. The mean pulmonary artery pressure was 24 mmHg and there was no right ventricular gradient or mitral regurgitation.

While she was walking in the hospital accompanied by one of us (WM) the patient complained of palpitation and breathlessness. The pulse was found to be rapid and jerky and a systolic murmur was present. Though the patient sat down, the symptoms persisted. Over a period of two minutes the pulse became impalpable, the murmur disappeared, and the patient then lost consciousness. Despite external cardiac massage peripheral pulses were not palpable and signs of anoxia developed. She remained unconscious for 90 seconds, after which she recovered spontaneously with a gradual restoration of the peripheral pulses and the systolic murmur. There were no neurological sequelae. During this episode the patient was wearing an electrocardiographic recorder. This disclosed an increasing sinus rate over three minutes, from a baseline of 70 beats/minute to a maximum of 130

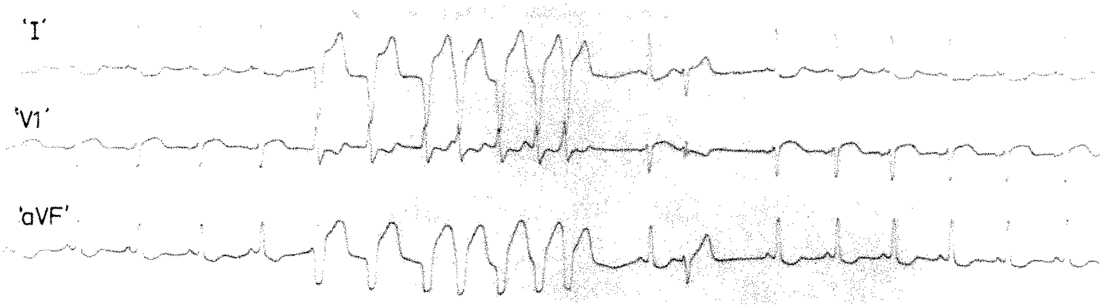

Fig. 1 *This is one of 12 episodes of ventricular tachycardia which were recorded during six days of three channel ambulatory electrocardiographic monitoring. The longest episode of ventricular tachycardia was 10 beats and the maximum heart rate never exceeded 160 beats/minute. The peak hourly and daily ventricular extrasystole count was 36 and 163, respectively.*

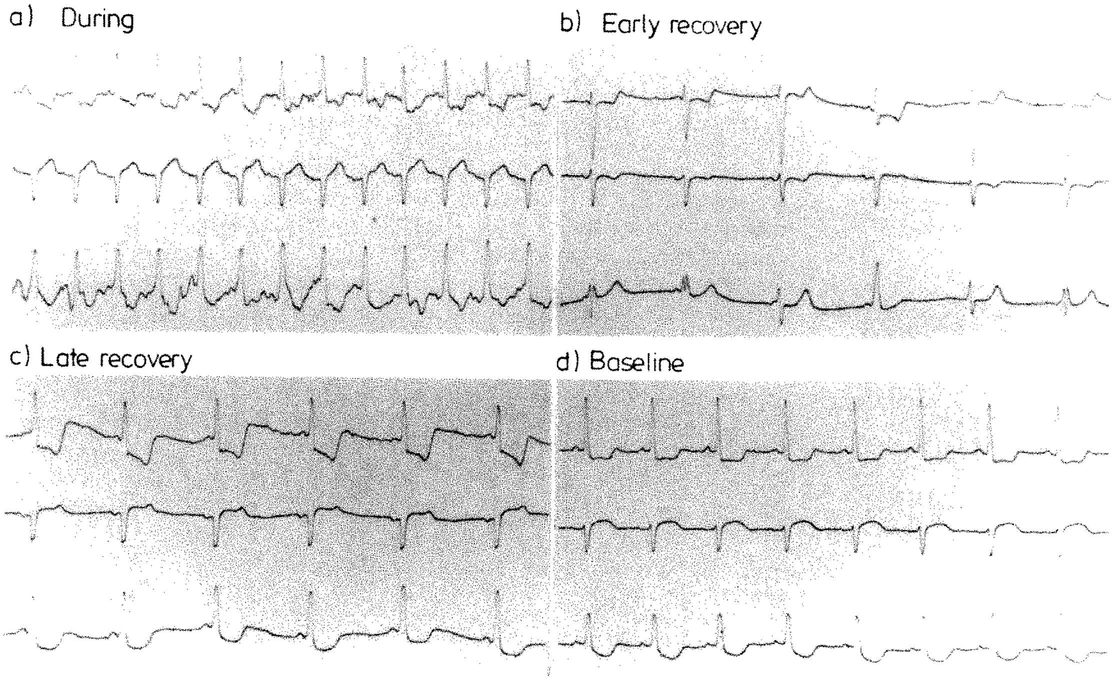

Fig. 2 *Three channel ambulatory electrocardiographic monitoring. (a) Sinus tachycardia 130 beats/minute during syncope; (b) atrioventricular dissociation with a junctional rhythm (beats 1, 3, and 5) and varying degrees of fusion with sinus impulses (beats 2, 4, and 6). Ventricular rate 50 beats/minute; (c) restoration of sinus rhythm with pronounced ST segment change; (d) this trace was taken earlier in the day and was identical to the pattern to which she returned three minutes after the episode.*

beats/minute at the time that she lost consciousness (Fig. 2). During the recovery period, ST segment depression was more pronounced and she showed atrioventricular dissociation with an accelerated junctional rhythm of 50 beats/minute and occasional fusion beats (Fig. 2); the sinus rate gradually accelerated with a return to normal sinus rhythm (70 beats/minute) but with pronounced ST depression (Fig. 2). Within three minutes the electrocardiogram had returned to the baseline pattern.

The patient was started on verapamil 120 mg daily. After three days, however, she complained of more frequent episodes of palpitation, breathlessness, chest heaviness, and dizziness and she was found to be in pulmonary oedema. Verapamil was discontinued, the pulmonary oedema cleared, and amiodarone was started with a loading dose of 1200 mg daily for one week followed by a maintenance dose of 400 mg daily. The patient improved and four months later she remains well and has had no palpitation or syncope. She continues to experience breathlessness and heaviness in the chest on effort. Seventy-two hour ambulatory electrocardiographic monitoring disclosed no ventricular tachycardia and a peak hourly and daily ventricular extrasystole count of three and nine, respectively. Treadmill exercise testing was repeated and she exercised for nine minutes, completing stage three of the Bruce protocol without distress.

Discussion

This patient has hypertrophic cardiomyopathy with rapidly progressive symptoms, syncope, and ventricular tachycardia; all features that are associated with poor prognosis.[2 3] Though it is logical to assume that syncopal episodes may be caused by arrhythmia this patient demonstrates that this need not be so. Ventricular tachycardia is a marker of severe disease and is often present in patients who have syncope and die suddenly.[2 3] It is clear, however, that other causes of syncope and sudden death operate.

The precise mechanism causing syncope in our patient is unknown. The episode was preceded by sinus tachycardia without definite ST changes, though in the presence of pre-existing repolarisation abnormalities ST change is difficult to assess. The loss of murmur and peripheral pulse was probably the result of left ventricular cavity elimination and a sudden decrease in stroke volume. Whether this was primarily the result of an acute decrease in afterload or in preload or the result of a reflex or metabolically mediated decrease in compliance or of some other mechanism is uncertain.

Though previous reports have suggested good symptomatic relief and improved exercise tolerance with verapamil,[10] this has not been our experience.[11] While on verapamil this patient developed left ventricular failure which cleared and has not recurred since verapamil was discontinued. The selection of the patient may be very important; the identification of those patients with hypertrophic cardiomyopathy who may benefit from verapamil requires further examination.

Amiodarone improved the symptoms and exercise tolerance and abolished serious ventricular arrhythmia in our patient. The potent antiarrhythmic effect of amiodarone in hypertrophic cardiomyopathy has been demonstrated.[11] Further work to characterise the effect of amiodarone on ventricular function and exercise tolerance is in progress.

We thank Dr Michael Jay for referring the case to us.

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Br Heart J 1982; **47**: 180–2

Survival after subacute cardiac rupture

S A QURESHI,* T RISSEN,† K E GRAY

From Barnet General Hospital, Barnet, Herts, and the Cardiothoracic Surgical Unit, Middlesex Hospital, London

SUMMARY A 43-year-old man collapsed suddenly, with pericardial tamponade, seven weeks after an inferior myocardial infarction. Pericardiocentesis disclosed very heavily blood stained fluid. Left ventricular angiography 10 days later showed a left ventricular aneurysm. At operation a left ventricular false aneurysm was resected and the patient recovered uneventfully.

Cardiac rupture occurs in 4 to 24% of all deaths from acute myocardial infarction.[1] It may occur from a few hours to several days after the infarction and is usually fatal. It is not usually an acute "blowout", but a gradual penetration of the necrotic myocardium by a dissecting haematoma,[1] leading to cardiac tamponade. Surgical treatment of this complication has occasionally been successful. We report a case of cardiac rupture that occurred seven weeks after myocardial infarction and was subsequently treated surgically.

Case report

A 43-year-old mechanic was admitted to hospital with a two day history of praecordial pain radiating down both arms and up to the throat. The pain was intermittent but had gradually increased in intensity. There was no significant past medical history.

On physical examination his general condition appeared good. His pulse rate was 80 per minute, regular, and his blood pressure was 160/110 mmHg. There was no evidence of cardiac failure. The electrocardiogram confirmed an acute inferior myocardial infarction. The chest *x*-ray film showed slight cardiomegaly. From day one to day three, his daily aspartate transaminase levels were 23, 38, 50 IU/l (normal <18), and hydroxybutyrate dihydrogenase levels 172, 310, and 290 IU/l (normal <140). He made an uneventful recovery and was discharged home seven days after admission, his blood pressure having settled to 120/70 mmHg. On review as an outpatient four weeks later, he was asymptomatic and his blood pressure was 140/95 mmHg.

Two weeks later, he had a sudden onset of dizziness followed by two transient syncopal episodes. This was soon followed by upper chest pain which radiated to the throat and was aggravated by deep inspiration and lying flat. On examination he was pale, cold, clammy, and dyspnoeic. Pulse was 120 per minute, regular, and of low volume. The systolic blood pressure by palpation was 70 mmHg on expiration, falling to 50 mmHg on inspiration. The jugular venous pressure was raised 8 cm above the sternal angle. The heart sounds were inaudible. The electrocardiogram showed the presence of the previous inferior myocardial infarction. An anteroposterior portable chest *x*-ray film showed probable cardiomegaly. An echocardiogram showed a large echo-free space anteriorly and posteriorly, indicating a pericardial effusion.

A diagnosis of pericardial tamponade was made and pericardiocentesis was carried out using the apical approach. On removal of 67 ml heavily blood-stained fluid, there was a dramatic clinical improvement and the blood pressure rose to 110/70 mmHg. The pericardial fluid haemoglobin was 10·4 g/dl and the circulating blood haemoglobin was 14·4 g/dl; the erythrocyte sedimentation rate was 22 mm/hour. He was transferred by ambulance to the Middlesex Hospital Cardiothoracic Surgical Unit, with a pericardial drain *in situ* but closed off. His general condition continued to improve so operation was deferred.

Left ventricular angiography, 10 days after his collapse, showed a large saccular posteroinferior left ventricular aneurysm (Fig.). This showed paradoxical movement and there was a suggestion of mural thrombus within it. Coronary arteriography showed a normal left coronary artery and a right coronary artery which was totally obstructed distal to the right ventricular branch.

At operation, 17 days after his collapse, excision of

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*Present address: Harefield Hospital, Middlesex.

†Since this paper was written Dr Rissen has died.

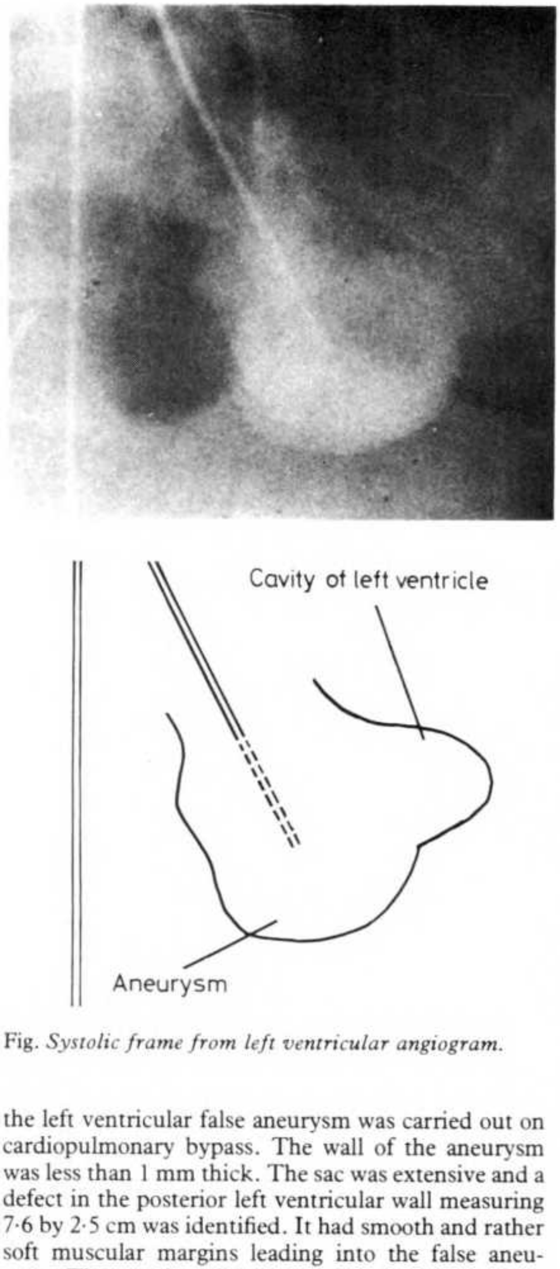

Fig. *Systolic frame from left ventricular angiogram.*

the left ventricular false aneurysm was carried out on cardiopulmonary bypass. The wall of the aneurysm was less than 1 mm thick. The sac was extensive and a defect in the posterior left ventricular wall measuring 7·6 by 2·5 cm was identified. It had smooth and rather soft muscular margins leading into the false aneurysm. The margins of the sac were separated from the heart and the ventricular defect closed with interrupted 2/0 Mersiline sutures and reinforced with a running suture superficially.

Postoperatively he was hypertensive and was treated with a nitroprusside infusion. His subsequent course was uneventful and he was discharged home two weeks after operation. He remains well six months later.

Discussion

Cardiac rupture usually leads to rapid deterioration and death within a period of minutes to hours, because of cardiac tamponade. Efforts to identify the causes of rupture have been inconclusive. Rupture is more common in the elderly, being commonest in the seventh and eighth decades,[2] and rare below 50 years of age.[3] Women are more likely to suffer cardiac rupture than men.[4] About 50% of ruptures occur within the first three days after myocardial infarction.[2]

Cardiac rupture is not usually an acute "blowout" phenomenon but is a gradual process that begins with small epithelial tears, which permit the formation of a haematoma that dissects through the necrotic myocardium. Death results from cardiac tamponade rather than pump failure.[1]

Repeated and prolonged chest pain may frequently precede cardiac rupture[2] and is thought to be the result of slow leakage of blood into the pericardial sac.[5] A possible complication of this is the formation of a left ventricular false aneurysm which, in contrast to a true aneurysm, may rupture and lead to death.[5]

The physical signs consist of sudden hypotension, rapidly increasing venous pressure, pulsus paradoxus, deepening cyanosis, and stupor. Abrupt onset of bradyarrhythmias in patients with acute transmural myocardial infarction showing sudden syncope should arouse suspicion of cardiac tamponade.[6] Echocardiography in this situation is extremely helpful as it is a rapid, non-invasive method of confirming a pericardial effusion.

We have found reports of successful surgical repair in 11 cases of cardiac rupture.[1 7-9] Once the diagnosis is made the most important step is pericardiocentesis. A drain may be left in the pericardial sac during transport to the theatre or even during interhospital transfer.

In this case the improvement occurring after pericardiocentesis was maintained, so emergency surgery was not needed and repair was undertaken as an elective procedure.

We wish to thank Mr M F Sturridge for providing the details of the operative findings.

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A major portion of hypertension investigation and consequent breakthroughs consist of clinical trials with approved drugs and studies of reviews of series of patients receiving "standard" treatment. The enormous upsurge in this research has created the need for a *single authoritative volume* to encompass the most important new information on the treatment of the hypertensive patient. *John Laragh, Fritz Bühler, Donald Seldin* and *more than 250* of the world's leading investigators from 19 nations – including three from the U.S.S.R. – have met that need with this groundbreaking presentation.

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Br Heart J 1982; 47: 183–5

Persistent right sinus venosus valve

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SUMMARY A 13-year-old girl presented with clinical features of pulmonary stenosis and regurgitation. Haemodynamic studies suggested the presence of a right ventricular tumour. M-mode and two dimensional echocardiograms indicated one or probably two soft thin walled structures originating from the right atrium. At operation a persistent right sinus venosus valve was removed.

One earlier case report described the M-mode echocardiographic features of this condition in a neonate who died shortly after operation. This report illustrates that a large persistent right sinus venosus valve may present clinically years after birth. Echocardiography played an important role in making the diagnosis.

At one stage during the life of the embryo the right valve of the sinus venosus almost divides the right atrium into two chambers. Normally this structure regresses some time between the ninth and 15th week. Its cephalic portion remains as the crista terminalis; its caudal portion, being divided by the left horn of the sinus venosus, remains as a valve of the inferior vena cava (Eustachian valve) and the valve of the coronary sinus (Thebesian valve).

The appearance of the valves can vary from a simple muscle bar to a fenestrated membrane or to a Chiari's network. These variations have been described extensively by Kauffman and Andersen[1] and Yater.[2] Large membranes in the right atrium, however, are rare. Persistence of the right sinus venosus valve can be associated with hypoplasia or atresia of the tricuspid and/or pulmonary artery orifice.[1–4] One case described by Gerlis and Anderson[5] also had an imperforate Ebstein malformation of the tricuspid valve. Echocardiographic M-mode features of this phenomenon have been reported once.[6] The appearance in diastole of a cloud of echoes in the tricuspid valve orifice and in the right ventricular outflow tract has also been reported.[6]

This report describes the haemodynamic, echocardiographic, and surgical findings in a case of persistent right sinus venosus valve presenting with unusual clinical findings of pulmonary stenosis and regurgitation.

Case report

A 13-year-old girl was known to have a systolic murmur since birth. In 1975 she was catheterised and valvular pulmonary stenosis and regurgitation were diagnosed.

She was admitted to hospital in 1979 to evaluate her progressively limited exercise capacity. On examination she was a thin girl, 144 cm in height and 29 kg in weight. Her lips were mildly cyanosed. The peripheral pulses were normal and peripheral oedema was not present. Her blood pressure was 115/80 mmHg, with a heart rate of 80 beats per minute. The first sound was closely split. A grade 4/6 rough mid-systolic murmur was audible in the second intercostal space at the left sternal border. In addition, a grade 3 protodiastolic murmur was heard best in the third intercostal space. The second heart sound was split. These findings were confirmed by phonocardiography.

Chest x-ray film showed normal heart size, with dilatation of the pulmonary conus. Electrocardiography showed a PR interval of 0·18 second and evidence of right atrial and ventricular hypertrophy.

The M-mode echocardiogram, performed with the Echocardio Visor single element, showed multiple "blurred" echoes in diastole posterior to the anterior leaflet of the tricuspid valve (Fig. 1A). These echoes were also seen in the right ventricular outflow tract. There was no interval between the tricuspid valve opening and the appearance of these "blurred" echoes. At the level of the pulmonary valve a discrete echo structure lying anterior to the valve was detected. This echo structure moved posteriorly with the onset of systole, shortly after the opening of the pulmonary valve (Fig. 1B, see arrow).

When the heart was examined with a dynamically focused Multiscan system,[7] an abnormal thin walled

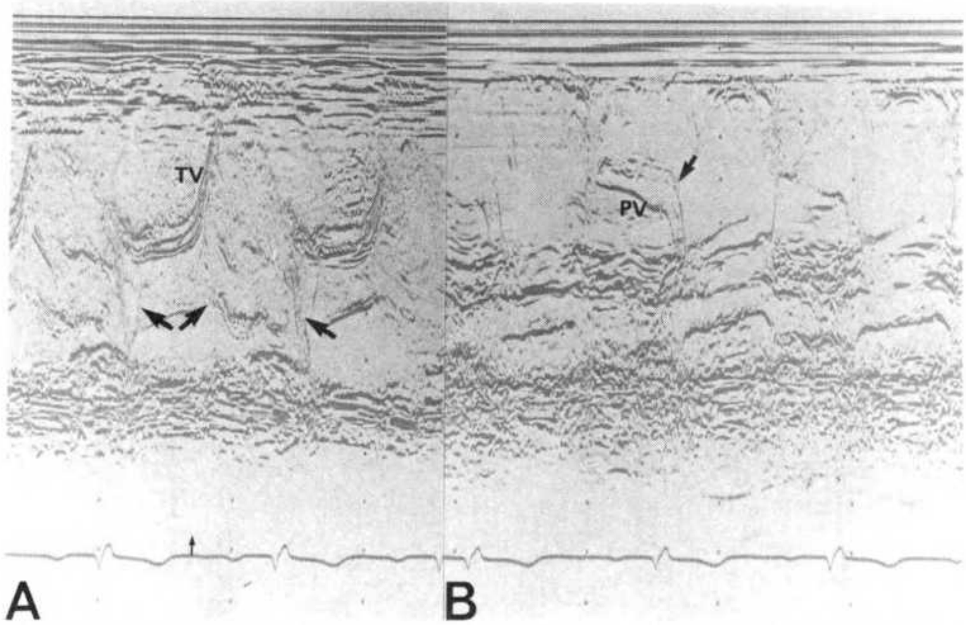

Fig. 1 *M-mode echocardiogram of the persistent membrane. (A) shows a cloud of echoes in the tricuspid valve (TV) orifice (arrows). At the level of the pulmonary valve (B) one single echo structure could be detected, being anterior to the pulmonary valve (PV), which moves posteriorly in systole after a short interval (arrow).*

soft tumour could be seen attached to the inner surface of the right atrium. As seen by the four chamber view, this tumour entered the right ventricle during diastole. Using the sagittal right ventricular outflow tract view, multiple echoes were seen crossing the pulmonary valve during systole (Fig. 2A).

Haemodynamic studies disclosed an increased right ventricular pressure of 70 mmHg (50 mmHg in 1975). Pulmonary regurgitation of 27 per cent, measured with a flow velocity probe, was present. No intracardiac shunts were detected. An angiogram of the pulmonary artery showed filling of the pulmonary artery and right ventricular outflow tract. In addition, a pendular structure of low density could be seen moving up and down in the right ventricle (Fig. 2B). A contrast injection in the right ventricle disclosed a heavily trabeculated ventricle. Situated close to the tricuspid valve there was a round tumour which appeared to be freely mobile. In addition, the valve proved to be mildly regurgitant. Review of the angiographic data obtained in 1975 showed that the tumour was already present, but considerably smaller in size.

It was concluded, therefore, that a benign flexible moving tumour was present, probably originating from within the right atrium.

At operation a large membrane representing a persistent right sinus venosus valve was found and resected. The pulmonary valve was normal. The white finger-like membrane measured 7 by 3 cm. Three broad-stalked cut edges were recognised; they were fenestrated, as were the free edges between them. Histological examination showed that the membrane consisted of a collagenous connective tissue covered by thin endocardium.

Discussion

The appearances of a persistent right sinus venosus valve vary considerably. Usually a simple muscle bar is present, as large membranes are rare. Associated abnormalities, such as hypoplasia or atresia of the tricuspid and or pulmonary valve, are also rare.

This report illustrates the clinical and echocardiographic features of a persistent right sinus venosus valve without associated cardiac anomalies.

The M-mode echocardiographic features of a persistence of the right sinus venosus valve seen in a newborn infant have been reported on only one occasion.[6] These features, as with those obtained in patients with right atrial myxoma, appear as a cloud of echoes penetrating the right ventricle during diastole.

Usually these echoes appear posterior to the anterior leaflet of the tricuspid valve. There is a slight time interval between the opening of the valve and the prolapse of the tumour into the tricuspid valve orifice.

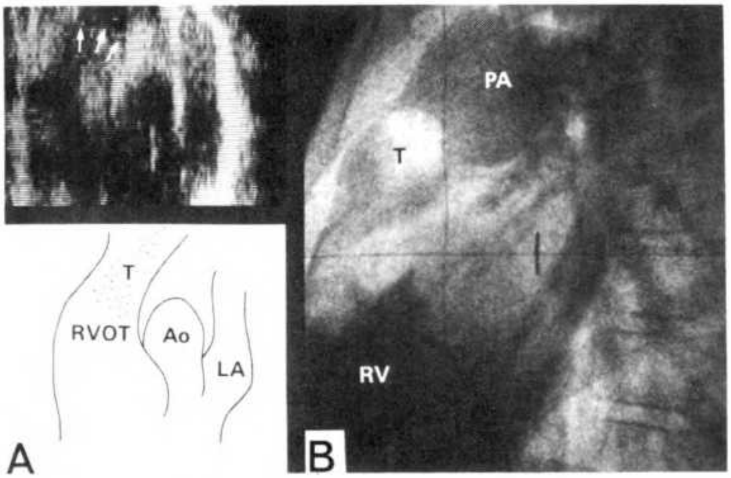

Fig. 2 *Two dimensional systolic image with diagram illustrating the right ventricular long axis view (A) which correlates with the angiocardiogram of the right ventricle (B). In (A) a cloud of echoes representing the tumour (T) was seen moving up and down in the right ventricular outflow tract (RVOT). In (B) the tumour was seen as a pendular low contrast structure in the RVOT and crossing the pulmonary valve in systole. Arrows indicate the top of the tumour. (RV, right ventricle; PA, pulmonary artery.)*

In our patient, however, this interval could not be recorded on M-mode echocardiography. Moreover, the cloud of echoes was not only present in the tricuspid valve orifice, but also appeared in the right ventricular outflow tract. The tumour was also seen passing the pulmonary valve as, in diastole, a single echo structure was present anterior to the pulmonary valve, which moved posteriorly shortly after its opening.

The real-time two dimensional four chamber view clearly showed a thin walled tumour attached to the inner surface of the right atrial wall. It crossed the tricuspid valve during diastole. Using the right ventricular long axis view a pendular tumour mass was seen in the right ventricular outflow which traversed the pulmonary valve. It was uncertain from these echocardiographic findings whether one or two soft thin walled tumours were present. Haemodynamic and angiographic data in 1975 had established a diagnosis of valvular pulmonary stenosis and regurgitation but the final studies in 1979 confirmed the presence of a soft tumour in the right ventricular cavity, which, in itself, caused the pulmonary obstruction.

At operation a large persistent right sinus venosus valve was removed successfully. Explanation for the absence of the interval on the M-mode echocardiogram between the appearance of the blurred echoes and the opening of the tricuspid valve must be related to the size of the persistent valve. This valve probably remained present within the right ventricular cavity and did not return to the right atrium in systole.

Our observations indicate that echocardiography is helpful in diagnosing this rare right atrial anomaly. The important features are the presence of multiple echoes which on the M-mode tracing appear posterior to the anterior tricuspid valve leaflet, while two dimensional echocardiography may visualise the structure at its site of atrial attachment.

It is fair to conclude, however, that the final diagnosis, and, in particular, its differentiation from other atrial "tumours", can only be established at operation.

We are greatly indebted to Professor V H de Villeneuve of the Sophia Children's Hospital, Rotterdam, for providing the clinical data which enabled us to study and describe the results in this patient.

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Correspondence

Br Heart J 1982; 47: 186–7

Lignocaine therapy in myocardial infarction

Sir,

The study of Pentecost *et al.*[1] on lignocaine therapy in the management of myocardial infarction may easily lead to the general conclusion that lignocaine is of more harm than benefit to the patient. In our opinion this conclusion cannot be drawn from the data presented.

Firstly, in this study one has to distinguish between ventricular fibrillation complicating pump failure and primary ventricular fibrillation. It is known from experience, that lignocaine is less effective in preventing the former than the latter. It is not clear from the description how many patients had pump failure, but judged from the stated hospital mortality (50%), it was probably a considerable number.

Secondly, the dosage of lignocaine in the first and second period of investigation was clearly below that proven to be effective.[2] Withholding such an inadequate regimen in the later years of study therefore cannot influence the incidence of ventricular fibrillation and thus only proves that inadequate treatment with lignocaine is no better than no treatment at all. The observed incidence of ventricular fibrillation (8 to 9%) in all three study periods is equal to the expected incidence in untreated patients in a coronary care unit.[3]

Thirdly, patients with compromised hepatic clearance remain suitable for treatment. After a loading period, gradual tapering down of the doses creates a plateau level, thus avoiding blood levels at which major toxicity occurs. When in doubt hepatic clearance can be predicted by indocyanine green clearance[4] and plasma levels can be determined quickly by enzyme immuno-assay.[5]

There is therefore no reason to withhold lignocaine treatment in any patient at risk for fear of major toxicity.

Pentecost's point that in ventricular fibrillation complicating pump failure the final outcome is determined by the extent of myocardial muscle loss and not by the initial success of defibrillation is well taken. In situations of suboptimal coronary care, however, or in the prehospital phase of acute myocardial infarction, adequate lignocaine treatment to prevent primary ventricular fibrillation may prove effective, safe, and indeed lifesaving.

Rudolph W Koster and Donald C Harrison,
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This letter was shown to Dr Pentecost who replies as follows.

Sir,

In our study we were concerned with the use of lignocaine to suppress ventricular extrasystolic activity, not with routine prophylaxis. The former practice is still followed in many hospitals where the suppression of "warning arrhythmias" is regarded as effective in the prevention of ventricular fibrillation. Our data suggest that this belief may not be justified. The important consideration concerning lignocaine dosage in this context is surely that the dose used was sufficient to suppress extrasystolic activity. In the review we did not distinguish between primary and secondary ventricular fibrillation because we were reporting what happened in routine clinical practice rather than describing a formal trial conducted within a highly selected group of patients. The distinction between primary and secondary ventricular fibrillation is, moreover, somewhat artificial.

Your correspondents appear to be advocating routine lignocaine infusion for all patients with myocardial infarction. Even if their reassurances concerning the use of this drug are justified, and relatively few hospitals will have access to indocyanine green clearance and plasma lignocaine levels, there is no available evidence of benefit upon which to base such a therapeutic policy. Even the trial which appears to be the spring-board for the enthusiast's approach to lignocaine prophylaxis based its message upon less than 30% of all patients presenting with suspected myocardial infarction—that is the population studied was highly selected. The conclusions cannot be extrapolated to all patients.

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THE AUTUMN MEETING of the British Cardiac Society took place at the Wembley Conference Centre, London, on Monday and Tuesday, 7 and 8 December 1981. The President, M F OLIVER, took the Chair during private business. At the scientific sessions the Chair was taken by T D V LAWRIE.

Abstracts of papers

Micro anatomy of acute occlusive coronary thrombi

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Eighteen occlusive thrombi identified by post-mortem coronary arteriography have been reconstructed in their entirety from serial histological sections.

Two forms of occlusive thrombi have been identified. The most common (15/18) is related to the break up of an atheromatous plaque allowing dissection of blood into the intima. Platelet rich thrombus forms over the exposed lipid both within the intimal dissection track and within the vessel lumen. Subsequent propagation of fibrin-rich thrombus occurs along the lumen. The break up of the plaque cap as shown by serial reconstruction is of far greater magnitude than previously suggested by the term plaque fissuring or cracking. The morphological appearances of the plaque rupture and intimal dissection suggest they occur over an appreciable period and may be responsible for the prodromal pain preceding the onset of acute myocardial infarction. The plaques associated with rupture were all lipid-rich but not necessarily causing previous high grade stenosis. The second form of thrombus found in three cases occurred at points of high grade stenosis just distal to a major branch, but no plaque rupture or lipid exposure was involved. This form of thrombosis appears to follow either reduced or turbulent flow through areas of high grade stenosis.

Myocardial noradrenaline response to acute ischaemia

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Activation of the sympathetic nervous system to the heart may be an important factor initiating malignant ventricular arrhythmias, but we have recently shown that myocardial noradrenaline overflow does not occur during a 10 minute period of acute ischaemia when serious ventricular arrhythmias including ventricular fibrillation are common. One explanation might be a decrease in sympathetic neuro-transmission.

During low and high frequency (1 Hz, 10 Hz) stimulation of sympathetic nerves from the left stellate ganglion in an open-chested anaesthetised dog preparation with occlusion of the left anterior descending coronary artery ($n=7$), the rise in venous noradrenaline concentrations from ischaemic and non-ischaemic areas of myocardium was similar and not significantly different from responses before coronary occlusion. At constant heart rate, blockade of neuronal re-uptake (desmethylimipramine 2·5 mg/kg, $n=5$) and attenuation of presynaptic alpha-adrenoceptors (yohimbine 1 mg/kg, $n=6$) significantly potentiated spontaneous and nerve stimulation-induced noradrenaline overflow from ischaemic myocardium. Neuronal noradrenaline re-uptake (by comparison of overflow before and after desmethylimipramine) was enhanced across ischaemic myocardium at 1 Hz but not at 10 Hz stimulation ($p < 0{\cdot}05$). Both drugs increased the incidence of spontaneous ventricular fibrillation or shortened the duration of occlusion before ventricular fibrillation compared with control observations.

Thus, sympathetic responsiveness is maintained and increased neuronal re-uptake and alpha-receptor negative feedback effects probably explain the lack of spontaneous noradrenaline overflow from the ischaemic myocardium.

Differential effects of intracoronary nifedipine on myocardial function and coronary flow in man

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Little is known about the direct effects of nifedipine on left ventricular myocardial function and coronary circulation in man. Therefore, the dynamic relations between left ventricular rate of pressure rise (max dP/dt) and fall (min dP/dt) and coronary sinus blood flow (CSBF) were studied after direct injection of 0·1 mg nifedipine into the bypass graft to the left anterior descending artery in eight and into the left coronary artery in one patient. Simultaneous measurements of coronary sinus blood flow by thermodilution and of high fidelity left ventricular systolic (LVSP) and end-diastolic (LVEDP) pressure were performed for 10 minutes. The changes in percentage of control ($^*p < 0{\cdot}05$) are given in the Table.

% changes:	*20 s*	*40 s*	*60 s*	*3 min*	*5 min*	*10 min*
LVSP	− 8*	− 9*	− 7*	0	− 1	−2
LVEDP	+36*	+56*	+47*	+11*	+ 4	−7*
max dP/dt	−15*	−17*	−14*	+ 1	+ 1	−1
min dP/dt	−18*	−23*	−17*	0	0	−1
CSBF	+19*	+28*	+28*	+19*	+14*	+7

Nifedipine injection produced a decrease in left ventricular systolic pressure and a severe increase in left ventricular end-diastolic pressure for 60 seconds. Both max dP/dt and min dP/dt were reduced for 60 seconds, whereas coronary sinus blood flow remained high for five minutes. After intracoronary nifedipine, changes in coronary sinus blood flow persisted long after changes in left ventricular function had subsided, suggesting differential effects of nifedipine on cardiac muscle and coronary arteriolar smooth muscle.

Early intervention in myocardial ischaemia

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Some recent reports have shown that early beta-adrenergic blockade in acute myocardial ischaemia reduces mortality and decreases the incidence of infarction. In a study involving 391 patients we found no difference in mortality or incidence of infarction at three months when patients were given intravenous beta-adrenergic blockade very early in their illness.

Over a 20 month period, patients admitted with a diagnosis of myocardial infarction or ischaemia were given intravenous metoprolol or placebo within six hours of the onset of symptoms and in the absence of contraindications. Intervention took place on a double-blind randomised basis and median delay time was two hours.

CK MB isoenzymes were measured eight hourly and log peak concentration used as an indirect measurement of infarct size. Mean log maximum CK MB was significantly lower in patients receiving metoprolol ($2{\cdot}08 \pm 0{\cdot}33$ standard deviation compared with $2{\cdot}17 \pm 0{\cdot}34$).

The percentage mortality at three months for patients given metoprolol was 8·1% and for patients given placebo 9·9%. The difference was −1·8%, with 90% confidence limits of −6·5% to 3%. While early intervention may reduce infarct size it is unlikely to affect early mortality. Long term follow-up will be needed to assess effect on remote prognosis.

Percutaneous transluminal coronary angioplasty

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Since January 1980 we have encountered 11 patients with single vessel disease and angina severe enough to recommend surgery, six of whom had rest pain with optimal therapy. We attempted angioplasty on the proposed day of surgery. Ten had anterior descending, and one right coronary stenosis. All had electrocardiographic evidence of reversible myocardial ischaemia, confirmed in nine who had thallium scintigrams. The stenosis was not crossed in four patients, and the vessel became occluded in two. It was crossed in seven and successfully dilated in six, a similar figure to the NHLBI registry. The artery occluded within five days in three of the successful dilatations, one of these having anterior infarction. Three left hospital symptom free with normal exercise electrocardiograms and scintigrams. Angina recurred in one at three months because of restenosis. Two are symptom free at two and 12 months. Six had operations on the same day, three with arterial occlusion. Two had operations later for angina. None of these developed postoperative Q waves or bundle-branch block.

Patients suitable for angioplasty are uncommon, the majority with single vessel disease being successfully treated medically. This disappointing outcome has not been previously reported but suggests the need for a cautious approach to the procedure.

Complications and results in eight patients undergoing percutaneous coronary angioplasty for very severe lesions

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Eight patients (seven men and one woman) aged between 28 and 70 years had single vessel stenosis with at least 90 to 95% obstruction. All had severe angina and five had rest pain. The right coronary artery was involved in two cases and the left anterior descending in the other six. One right coronary stenosis could not be crossed by the angioplasty catheter.

The initial gradient across the stenosis in the remaining patients averaged 65 mmHg, with the highest gradient of 105 mmHg. Up to 19 dilatations at five atmospheres were used with elimination of the gradient in all patients. The mean stenosis after dilatation was 25%.

In one patient a new technique using a detachable inflated balloon was used to close a large circumflex/bronchial fistula in addition to left anterior descending angioplasty.

Total obstruction of the major coronary artery by the balloon was symptomless in all patients for up to 25 seconds but five cases developed pain and ST segment elevation developed by 30 seconds.

Coronary artery spasm around the balloon occurred in three cases, despite nitrates and nifedipine. In one case this persisted for several minutes after the balloon was withdrawn and was accompanied by chest pain. The distal artery remained patent but a saphenous vein graft was placed prophylactically. No infarct occurred.

The six patients successfully dilated are all symptom free and have normal maximum exercise tests at periods of up to seven months after the procedure. All were maintained on anticoagulants, persantin, aspirin, nifedipine, and cardioselective beta-blockers for three months.

Persistent ischaemic disturbances of myocardium in patients with angina

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This study describes characteristics of myocardial ischaemia that may be relevant to morbidity and mortality. Twenty patients with angina pectoris and coronary disease underwent four days of ambulatory electrocardiographic monitoring for analysis of ST segment changes. Each patient was also studied using positron tomography to quantify the regional myocardial uptake of rubidium-82, with cold stimulation and supine exercise. The 24 hour electrocardiographic recordings showed between four and 20 episodes of significant ST depression (>1 mm) lasting between four and 28 minutes and only 21±5% (standard deviation) were symptomatic. Positron tomography and cold pressor showed regional decreases (18·5±5·2%) in cation uptake in nine patients; four showed ST depression, of whom only three had symptoms. All 20 patients showed an absolute decrease in cation uptake (33±9·4%) after exercise in one region of the myocardium, which persisted in serial scans for 42·4±10·1 minutes even though pain and the electrocardiogram returned to normal by 12·6±5·1 minutes. The 24 hour electrocardiogram showed frequent asymptomatic episodes of ST depression. Positron tomography showed prolongation of regional myocardial ischaemia beyond symptomatic and electrocardiographic evidence. Therefore, in patients with angina and coronary disease, the myocardium can be jeopardised for longer periods in each day than was previously suspected.

Fate of graft and native vessel after bypass of minor stenosis

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Minor stenosis of major coronary arteries (<50%) are not usually bypassed because of the fear that both graft and native vessel will occlude. We have reviewed a consecutive series of 63 postoperative coronary arteriograms in which the preoperative study showed at least one such stenosis, and examined the outcome in 41 vessels which were bypassed and in 67 which were not. The mean interval between operation and reinvestigation was 23 (range six to 75) months.

Seven of 67 unbypassed arteries had progressed to severe stenosis (five) or to occlusion (two). In 41 bypassed vessels 24 had patent grafts and native arteries, 12 had patent grafts and occluded arteries, five had occluded grafts and unchanged arteries, and none had occlusion of both graft and native vessel. None had ventriculographic evidence of new infarction in the grafted territory.

Grafts to vessels with minor stenosis have no increased tendency to early occlusion, though they are associated with progression of the stenosis to occlusion. Bypassing minor stenoses does not prejudice the myocardium supplied.

Mechanisms of phase Ia and Ib early ventricular arrhythmias

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Two phases of early ventricular arrhythmias occur within the first 30 minutes of experimental myocardial ischaemia and may relate to mechanisms of sudden death in man.

These have been investigated by detailed mapping of regional myocardial blood flow and epicardial activation patterns at onset of phase Ia and Ib arrhythmias five and 17½ minutes, respectively, after high ligation of the left anterior descending coronary artery in seven open chest anaesthetised dogs. Epicardial activation patterns were determined by multiplexing signals from an 80 point electrode grid, blood flow using tracer microspheres, and three dimensional computer maps constructed.

The myocardium was subdivided into central ischaemic (below 25%), border ischaemic (25 to 75%), and non-ischaemic (over 75%) flow areas. Flow in the central ischaemic and normal areas was unaltered during the two phases of arrhythmias, but border area epicardial flows were greater ($p<0{\cdot}05$) during phase Ib than phase Ia.

Activation maps showed delayed and fragmented activation in the central ischaemic area (51·2 ± 16·6 ms) during phase Ia arrhythmias. These were significantly less ($p<0{\cdot}05$) during phase Ib (42·6 ± 12·1 ms).

These data support the concept that phase Ia arrhythmias are re-entrant whereas phase Ib arrhythmias are not. Differences in conduction are not flow related, but modulation in border area flow may enhance washout of ischaemic metabolites.

Cellular electrophysiological changes associated with ventricular fibrillation during myocardial ischaemia and reperfusion

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Cardiac cellular electrophysiological changes associated with the development of ventricular arrhythmias during myocardial ischaemia are poorly understood. Using isolated guinea pig hearts we recorded cellular electrophysiological and surface electrocardiographic changes associated with the development of ventricular arrhythmias during myocardial ischaemia and reperfusion.

Ventricular tachycardia developed in 14 of 16 and ventricular fibrillation in three of 16 hearts at 18 ± 3 minutes after the onset of low flow myocardial ischaemia (coronary flow reduced to 10% of control for 30 minutes). In contrast, ventricular tachycardia occurred in only three ($p<0{\cdot}05$) and ventricular fibrillation was absent in 20 hearts subjected to zero coronary flow for 30 minutes. Reperfusion after 30 minutes of low flow caused ventricular fibrillation in 12 of 14 and in 19 of 20 hearts after zero flow. Action potential duration and $\dot{V}_{max}$ decreased and QRS duration and refractory period increased to peak values at 12 ± 3 minutes after the onset of low flow myocardial ischaemia. In all cases, however, spontaneous recovery preceded the development of ventricular arrhythmias, for example $\dot{V}_{max}$ from 36 ± 5·5 to 63 ± 4 V/s; QRS duration from 54 ± 8 to 46 ± 7 ms; refractory period from 186 ± 4 ms to 130 ± 4 ms. In contrast, during zero flow, when ventricular arrhythmias were significantly less, no improvement was observed. After reperfusion, ventricular fibrillation occurred at 73 ± 9 seconds and was always preceded by an increase in action potential amplitude (50 ± 3 to 77 ± 3 mV) and $\dot{V}_{max}$ (25 ± 5 to 42 ± 4 V/s), a further reduction in action potential duration (98 ± 7 to 86 ± 6 ms), and a reduction in QRS duration (130 ± 9 to 81 ± 9 ms) and refractory period (140 ± 10 to 120 ± 10 ms). Thus, an increase in $\dot{V}_{max}$, associated with a reduction in the QRS duration and refractory period, preceded ventricular fibrillation during myocardial ischaemia and reperfusion. The mechanism for the spontaneous electrophysiological recovery observed during low flow ischaemia is not yet clear; its absence during zero flow when arrhythmias are infrequent suggests that it may be arrhythmogenic.

Intravenous amiodarone: an effective antiarrhythmic agent

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Oral amiodarone has been used with success in the treatment of supraventricular and ventricular arrhythmias. It has a long half-life, and when administered orally may take three to five days to become effective. We investigated the acute antiarrhythmic properties of the intravenous preparation.

We studied six patients, two men and four women, whose ages ranged from 32 to 66 years. Five patients had paroxysmal ventricular tachycardia and one had paroxysmal atrial fibrillation. All were resistant to conventional medication. Holter monitoring was performed (with the patients on no treatment) for 24 hours before amiodarone treatment.

Intravenous admiodarone 300 mg diluted with 20 ml normal saline was administered over 10 minutes, and blood collected for plasma amiodarone levels at two, five, 10, 30, and 60 minutes after the onset of the infusion. Electrocardiograms were performed at rest, and at the same time intervals as above, and analysed for rate, rhythm, PR, QRS, and QTc values. A continuous, slow speed rhythm strip was recorded. Oral amiodarone in the recommended regimen was instituted immediately after the intravenous bolus. Plasma amiodarone levels and electrocardiograms were taken one, four, and 12 weeks later, with further Holter monitoring at three months.

During the intravenous amiodarone infusion, plasma levels rose, reaching their maximum at 10 minutes (for example 18·3 mg/l). They then fell fairly steeply, reaching levels of 1·1 to 1·3 mg/l at 60 minutes. Heart rate fell slightly but not significantly in all patients and there was no significant change in the blood pressure or the PR and QRS values. The QTc was lengthened in all patients, being increased by 8 to 20% of the resting values. The maximum QTc was achieved by two to five minutes after the onset of the infusion and persisted until 10 minutes. Resting values were regained by 60 minutes. The antiarrhythmic effect coincided with the maximum QTc, ventricular tachycardia and ventricular extrasystoles being abolished between two to five minutes after the intravenous amiodarone was started, and they did not recur within the 60 minutes period.

Thus intravenous amiodarone is an effective antiarrhythmic agent and can be administered without significantly affecting the pulse rate or blood pressure. The QTc is prolonged in all patients, maximum values coinciding with the onset of its antiarrhythmic action.

Amiodarone therapy: unwanted effects

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We reviewed 70 patients receiving amiodarone long term for refractory arrhythmias to assess the incidence and importance of unwanted effects and their relation to plasma drug levels. High performance liquid chromatography was used to measure levels of amiodarone (0·2 to 5·2 mg/l) and its desethyl metabolite (0·3 to 4·7 mg/l). Drug levels correlated with dosage (200 to 600 mg daily) (r 0·59, $p<0·001$) but not duration of treatment. Patients experiencing most side effects had the highest levels of amiodarone ($p<0·01$) and desethyl amiodarone ($p<0·01$) but the severity of individual effects did not correlate with drug levels. Photosensitivity (57%), tremor (40%), sleep disturbance (28%), and headaches (14%) were most common. Corneal lipofuscin deposits were universal but vision was unimpaired. Only one patient developed clinical hypothyroidism though free T4 was raised in five and decreased in two. This was not associated with an alteration in plasma drug levels. A rise in hepatic transferases (1·5 to 4 times normal) occurred in eight. Levels of parent compound (r 0·58, $p<0·001$) and metabolite (r 0·62, $p<0·001$) were highest in these patients. Serum bilirubin and alkaline phosphatase were not raised. Treatment was discontinued in six patients because of side effects: these resolved within one week and therapeutic efficacy persisted for one to two weeks. This suggests that, in keeping with its therapeutic action, the unwanted effects of amiodarone probably also reflect tissue deposition.

Does digoxin do any good in heart failure in sinus ryhthm?

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Doubt exists whether digoxin improves poor myocardial function. Nine patients with dilated cardiomyopathy and sinus rhythm whose heart failure was stable were studied non-invasively when off digoxin for at least two weeks and after two weeks of treatment (mean serum digoxin level 1·53 ± 0·57 mmol/l).

Systolic time intervals and echocardiographic dimensions were compared at rest during and off digoxin, and the effects of handgrip and symptom limited treadmill exercise were examined.

No change in symptoms, physical signs, body weight, systolic blood pressure, or heart rate occurred.

The left ventricular ejection time index (LVETI) fell in all ($p<0·001$) and PEP/LVET showed no consistent change. Echocardiographic left ventricular dimensions were 5·71 ± 1·72 cm at end-systole and 6·79 ± 0·83 cm at end-diastole and did not change, nor therefore did the stroke volume or ejection fraction from which they were derived. Neither the peak rate of shortening nor that of filling changed.

Handgrip exercise at 50% of maximum produced increases in blood pressure and heart rate which did not change after digoxin. The left ventricular ejection time index increased from 376·6 ± 14·5 to 390·69 ± 18·8 ($p<0·01$) before digoxin, with similar values after digoxin. A decrease in pre-ejection period index only reached significance after digoxin ($p < 0.01$) and accordingly PEP/LVET decreased after digoxin from 0·56±0·10 to 0·50±0·09 ($p < 0.01$). The changes in echocardiographic measurements were not significantly different after digoxin.

Treadmill exercise produced increases in blood pressure and heart rate which were unchanged after digoxin. Left ventricular ejection time index increased and pre-ejection period index decreased equally while on and after digoxin and accordingly the fall in PEP/LVET did not change.

Continuous electrocardiographic recording during the two hour studies showed an increase in both supraventricular and in ventricular ectopic beats while on digoxin.

It was concluded that digoxin exerted no beneficial effect on left ventricular performance either at rest or on exercise.

Inotropic action of digoxin is maintained with long term treatment

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Whether digoxin still exerts a positive inotropic effect with long term treatment remains controversial. Eleven patients (aged 46±3 years, mean±SEM; six men) with various types of heart disease, in sinus rhythm, treated with digoxin (serum digoxin 1·2—1·6 nmol/litre) for 10 months to nine years were studied on three consecutive days before and again six weeks after replacing digoxin with placebo and continuing other treatment. M-mode echocardiographic measurements showed significant ($p < 0.05$, paired t test) increases in left ventricular end-diastolic dimension (5·0±0·3 to 5·2±0·3 cm) and end-systolic dimension (3·5±0·3 to 3·8±0·4 cm) and a decrease in calculated mean circumferential shortening velocity (1·1±0·1 to 0·9±0·1/s), with non-significant reduction in fractional shortening velocity—analysis of variance showed no difference between measurements on consecutive days. Systolic time intervals, given as the difference between the observed value and that predicted for a normal subject of the same age and sex,[1] showed significant increases in the duration of electromechanical systole (−7·0±4·8 to +8·0±4·2 ms) and left ventricular ejection time (+7±6 to +17±7 ms), with a non-significant increase in pre-ejection period. A small non-significant increase in heart rate (81±5 to 83±7) was observed; blood pressure and body weight remained unchanged. Clinical deterioration occurred in one patient who improved again when digoxin was restarted. These findings indicate that the inotropic action of digoxin is indeed maintained with long term treatment.

Reference

[1] Weissler AM, Harris WS, Schoenfeld CD. Bedside technics for the evaluation of ventricular function in man. *Am J Cardiol* 1969; 23: 577–83.

Calcium handling by normal and diseased ventricular myocardium

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In patients undergoing cardiac catheterisation and investigations involving cardiac pacing, the left ventricular pressure and its maximum rate of rise ($LVdP/dt_{max}$) were recorded with a catheter tip manometer. After a period of atrial or ventricular pacing at a single steady frequency, a test pulse was introduced after a variable interval. The optimum interval for the contractile response was between 800 and 900 ms in 14 normals, seven patients with coronary artery disease, and three patients with cardiomyopathy; one further patient with cardiomyopathy had a short (650 ms) optimum interval. Two successive test beats were then studied, each preceded by the optimum interval. Potentiation of both these beats above the control contractile state was induced by a preceding premature depolarisation. $LVdP/dt_{max}$ of the second test beat was linearly related to $LVdP/dt_{max}$ of the first test beat. The slope of this relation was 0·52 to 0·70 in patients with normal myocardium and 0·20 to 0·48 in patients with myocardial dysfunction. In terms of calcium handling by myocardial cells, these results indicate that the time for recirculation of calcium from one beat to another is usually normal in diseased muscle, but the fraction recirculated is reduced.

Ergometrine-induced changes in left ventricular volume in patients with ischaemic heart disease

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Left ventricular volume (praecordial counting of

^{99m}Tc-labelled blood pool) and the 12 lead electrocardiogram were monitored continuously in 10 patients with ischaemic heart disease, in the basal state and after intravenous ergometrine (0·15 to 0·35 mg).

All patients developed progressive dilatation of the left ventricle over a period of 9·6±1·7 minutes, culminating in typical angina associated with diagnostic ST segment changes in six patients and trivial or no changes in four patients. The maximum percentage change in end-diastolic volume, end-systolic volume, stroke volume, and ejection fraction was 38±14, 10±49, −20±14, −37±12, respectively in the former group, and 31±15, 90±35, −7±12, −29±6 in the latter group. No significant changes were found in five normal subjects. All except one patient (with no electrocardiographic changes) had significant coronary atheromatous stenosis. In 10 episodes (two patients) of spontaneous myocardial ischaemia at rest with coronary artery spasm (shown by angiography) similar changes in left ventricular function were seen, but their onset was abrupt with rapid progression.

Angina may be accompanied by deterioration in left ventricular function without diagnostic electrocardiographic changes. The time course of left ventricular volume changes after ergometrine may be related, in part, to increase in left ventricular preload and may not be the result only of myocardial ischaemia.

Psychological sequelae of profound hypothermia and circulatory arrest in children subjected to open heart surgery before age of 2 years: blind controlled study

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The introduction of profound hypothermia and circulatory arrest, giving a still and bloodless operating field, has allowed earlier correction of congenital heart defects.

Concern still exists that absent cerebral circulation, even with profound hypothermia, may cause cerebral damage, despite several previous reports to the contrary, which can be criticised on methodological grounds. The present study was designed to overcome these criticisms, and yields very different results

Twenty-six children were studied who underwent cardiac surgery with profound hypothermia and circulatory arrest. These control groups were studied: (1) children with similar cardiac defects operated upon using continuous perfusion (15 children); (2) sibs of the hypothermia arrest group (12 children); (3) sibs of the continuous perfusion group (12 children).

All children were tested at age 5½ years by qualified psychologists using the "McArthy Scales of Childrens' Abilities".

The intelligence test scores of the hypothermic arrest group were significantly lower than those of the control groups (p<0·0017), Table.

	Mean IQ
Hypothermic arrest group	88·7
Control surgical group	99·5
Siblings of hypothermic arrest group	108·4
Siblings of control surgical group	96·3

These results contradict the reassuring conclusion of most other studies and suggest that hypothermic arrest should be used only when essential for safe correction.

Fate of aortic, pulmonary, and coronary anastomoses after anatomical correction of transposition of great arteries (TGA)

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Anatomical correction of transposition of the great arteries entails circumferential anastomoses of the aorta, and pulmonary and coronary arteries at a very young age. The fate of these anastomoses is of crucial importance for the long term results of this operation. In an attempt to clarify this, 15 patients were studied by repeat cardiac catheterisation and angiography one to 3·5 years (mean 1·5 years) after operation. The ages at the time of correction varied from 8 weeks to 9 years; 12 were below the age of 2 and six below the age of 1 year. There were no gradients recorded at the site of the aortic anastomosis, with angiographic evidence of normal growth in all patients. The coronary ostia were adequately visualised in all patients with no evidence of ostial stenosis or significant kinking of the proximal coronary arteries. For the pulmonary anastomosis it was necessary to use a dacron tube in three and a tube of homologous dura measuring 2·5 cm in diameter in 12 patients. This new non-valved conduit was placed on the right of the aorta in six and on the left in nine. Three patients had supravalvar pulmonary stenosis with a gradient of

30 mm or more. All these patients had the conduit placed on the right side.

It is concluded that the aortic and coronary anastomoses appear to grow satisfactorily, supravalvar pulmonary stenosis occurs only when the pulmonary artery is placed to the right of the aorta, and that large tubes of homologous dura allow for normal growth of the pulmonary artery.

Tetralogy of Fallot in adults—clinical features and long term surgical results

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Information on adults with tetralogy of Fallot is limited. Forty-six patients aged 20 to 45 years (mean 28·5 years) underwent total correction of tetralogy of Fallot in the 20 years to January 1980. Fifteen had undergone previous palliative surgery. As in children, dyspnoea and central cyanosis were the commonest features but, in contrast, cardiomegaly, audible P_2, anginal pain, and previous infective endocarditis were prominent. A right atrial "a" wave greater than 10 mmHg (17 patients) and right ventricular end-diastolic pressure greater than 9 mmHg (30 patients) were evidence of impaired right ventricular function. Aortic regurgitation was the commonest additional lesion. Additional aortic or tricuspid valve replacement (five patients) and a valved conduit from right ventricle to pulmonary artery (three patients) were required. Prolonged ventilation and bronchial collateral haemorrhage were the commonest postoperative complications. Hospital mortality was 6·5%. In 10 patients who were restudied the outflow gradient was less than 50 mmHg and the septal repair intact. Twenty-two of 24 patients followed for one to 19 years (mean 8·6 years) lead normal lives. In conclusion, adults with tetralogy of Fallot remain in need of total correction which can be performed safely with long term symptomatic improvement.

Isolated anterior mitral cleft; two dimensional echocardiographic assessment and differentiation from "clefts" associated with atrioventricular septal defect

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Congenital mitral regurgitation may result from various anatomical substrates, among which is isolated cleft of the anterior (aortic) leaflet. Though rare, this lesion is important because, unlike most forms of mitral regurgitation, it is eminently suitable for conservative surgical repair.

No previous method of investigation has enabled reliable recognition of this defect. It has been impossible to refer patients with mitral regurgitation for operation and be sure that mitral valve replacement will be unnecessary.

Using two dimensional echocardiography, five cases of isolated anterior mitral cleft have been identified in children with mitral regurgitation. The appearances were quite different from those of the "cleft" in the mitral valve of 30 patients with atrioventricular defects. Here the "cleft" between anterior and posterior bridging leaflets invariably pointed towards the ventricular septum, whereas isolated anterior mitral clefts always pointed towards the left ventricular outflow tract.

Four children underwent angiocardiography, which was not specific for the mitral abnormality. The fifth was operated upon without cardiac catheterisation. All had repair of the anterior mitral cleft. Only two had any residual regurgitation, and that was minimal.

Our current policy is therefore to operate on such patients without prior invasive studies if the regurgitation is more than mild.

Atrioventricular discordance—two dimensional echocardiographic study

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Atrioventricular discordance is associated with a spectrum of complex cardiac malformations including congenitally corrected transposition. Theoretically, two dimensional echocardiography should be the ideal technique to define this spectrum. Accordingly, 43 patients with atrioventricular discordance (33 laevocardia; 10 dextrocardia), all with correlative catheterisation data, were studied.

Two dimensional echo did not identify atrial morphology. Atrial situs (41 solitus, two inversus) was derived from high kV filter films. Right ventricular morphology was identified in 31 patients and left ventricular morphology in 36 patients. A common atrioventricular valve was present in two patients. In the remaining 41 patients, the right atrioventricular valve was visualised as bileaflet with paired chordae in 41 patients and the left valve as trileaflet in 29 patients. Complex atrioventricular valve malformations were identified in 14 patients. Reversed atrioventricular valve septal leaflet implantation occurred only in 11 patients with an intact atrioventricular septum (nine with no ventricular septal defect and two with isolated subpulmonary defects). In 30 patients where a perimembranous inlet defect excavated the atrioventricular septum, septal leaflet implantation was at a common level. A wide spectrum of abnormal ventriculoarterial connections was defined; (i) ventriculoarterial discordance (30 patients); (ii) single outlet (seven patients), and (iii) double outlet right ventricle (five patients).

We conclude that an integrated radiographic/two dimensional echocardiographic approach consistently defined atrioventricular discordance, revealing a much wider spectrum of associated malformations than those previously reported.

Systolic anterior motion of mitral valve: chordal or valve participation and its relevance to presence and degree of obstruction in patients with hypertrophic cardiomyopathy

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Two different two dimensional echocardiographic patterns of systolic anterior motion have been observed in patients with hypertrophic cardiomyopathy. In some patients the anterior and posterior leaflets of the mitral valve, chordae tendineae, and occasionally the anterolateral papillary muscle were seen to encroach in systole upon the left ventricular outflow tract. Chordae tendineae without involvement of the mitral leaflets were seen to cause systolic anterior motion in a second group. Other patients did not show systolic anterior motion. A retrospective blind study was performed to investigate the relevance of the different two dimensional echocardiographic patterns of valve participation to the presence and degree of obstruction and mitral regurgitation in 27 patients with hypertrophic cardiomyopathy. Obstruction was absent in six without systolic anterior motion. In 11 in whom the chordae alone were responsible for the systolic anterior motion the gradient averaged 10 mmHg (0 to 23). Ten with systolic anterior motion resulting from major participation of the leaflets were found to have a mean gradient of 81·4 mmHg (20 to 150). In all three groups mitral regurgitation was present: two of six without in the systolic anterior motion; four of 11 with systolic anterior motion caused by involvement of the chordae, and six of nine caused by the leaflets. In conclusion: (1) chordal or leaflet participation in systolic anterior motion is relevant to the presence and degree of obstruction; (2) leaflet involvement usually implies severe obstruction; (3) mitral regurgitation in hypertrophic cardiomyopathy may be the result of systolic distortion of mitral valve apparatus.

Assessment of neurons in dilated (congestive) cardiomyopathy: new concept of pathogenesis

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The aetiology of dilated (congestive) cardiomyopathy (COCM) remains unknown. Possible virological and immunological contributory factors have been suggested and evidence exists of parasympathetic dysfunction even in the early prefailure stage.

To confirm the physiological findings counting and assessment of neurons in right atrial strips (between the venae cavae) have been undertaken in seven patients with COCM and compared with similar strips from five normal individuals. The tissue was divided, blocked, paraffin embedded, and sectioned serially (7 μm thick). Every seventh section was stained with haematoxylin and eosin and intervening random sections with Miller's elastic van Gieson stain.

The results showed a significant reduction of the number of neurons in COCM: 4565 ± 471, compared with normal controls in whom 6412 ± 377 neurons were found ($p < 0·002$). Furthermore, morphological abnormalities, particularly in the amount of collagen tissue, were noted. Comparison with three known cases of Chagas's heart disease was also made.

It is concluded that depletion of neurons may be aetiologically related to COCM, possibly by a cell mediated immune response related to an initial viral infection and that neuronal depopulation is linked with evidence of parasympathetic dysfunction.

Emission computed tomography of lungs in pulmonary embolism

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Ventilation-perfusion lung scans obtained by conventional imaging and emission computed tomography (ECT) studies using standard radiopharmaceuticals (133 Xenon and ^{99m}Tc-MAA) were compared in 84 patients with suspected embolic lung disease. The Cleon-711 whole body emission tomographic scanner and the IGE 400T rotating gamma camera (with multiplane imaging capabilities) were used for emission section scanning. Data from pulmonary angiography were also available in a number of cases.

Concordant data were obtained in 72 cases (57 positive, 15 negative); results were discordant in 10 patients and two studies were indeterminate. In eight patients the conventional perfusion images appeared to be normal while ECT showed unequivocally the presence of perfusion deficits. Multiplane section imaging thus increased the sensitivity of lesion detection by 10% and excellent correlation was obtained between the ECT images and the data from pulmonary angiography.

Section scanning with ECT permitted display of the entire lung volume and clearer definition of the mediastinal space, with substantial improvement in image contrast and information with depth. This leads to increased accuracy in the detection of the extent of perfusion impairment. Image reconstruction of the lung in the coronal plane appears to provide optimal data for documentation of segmental perfusion defects, and emission computed tomography appears to have a promising future in the detection of embolic lung disease.

Drug-induced modulation of low density lipoprotein receptor in man

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High circulating low density lipoprotein levels, as found in type II hyperlipoproteinaemia, predispose to premature and severe coronary atherosclerosis. This study describes, in 12 such subjects, the effects on low density lipoprotein metabolism of two hypolipidaemic drug regimens.

Bezafibrate (B, 600 mg/d) significantly lowered total plasma cholesterol by reducing circulating levels of very low density lipoproteins and low density lipoprotein (by 30% and 11%, respectively). The hypolipidaemic action of cholestyramine (C, 24 g/d) was confined to low density lipoprotein cholesterol which fell 33% during treatment. Neither drug affected high density lipoprotein cholesterol.

The kinetic variables of low density lipoprotein metabolism were measured in the type II subjects before and during administration of the drugs. Both B and C increased the plasma fractional clearance rate of low density lipoprotein by 16% and 29%, respectively. This was the result entirely of a 65% and 100% increase in receptor mediated catabolism of the lipoprotein. Its fractional removal rate by the receptor independent pathway remained the same.

We conclude that despite their differing actions on HMG CoA reductase and bile acid metabolism, both drugs induce qualitatively similar changes in low density lipoprotein receptor activity.

Isolated human heart cells

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The isolation of human cardiac myocytes from tissue excised during the treatment of patients by cardiac surgery has permitted preliminary study of their electrical activity and responses to catecholamines.

The technique for isolating the cells has been developed from similar methods employed for rat, guinea-pig, and canine tissue, and involves incubation of chopped tissue in a series of solutions containing trypsin and collagenase.

In six separate experiments, good yields of myocytes have been obtained from samples of right ventricular infundibulum of children (4 to 10 years) undergoing correction of Fallot's tetralogy. The isolated cells are 60 to 140 μm long, 10 to 30 μm wide, and have typical cardiac morphological characteristics. They are capable of generating action potentials from resting membrane potentials of -76 ± 7 mV (mean ± SD: n = 12) and can be paced electrically. Administration of catecholamines produced a rise in the plateau phase of the action potential, consistent with responses observed in vivo.

We think this technique can be developed to provide another index of myocardial preservation during cardiac surgery.

Cardiac arrhythmias and electrocardiographic changes related to hypoxaemia in heavy smokers and in patients with chronic obstructive airways disease

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Heavy smokers with ischaemic heart disease and patients with chronic obstructive airways disease are known to have a high incidence of cardiac arrhythmias. Since hypoxaemia is common to both groups, we recorded continuous modified V5 lead through Medilog 2 recorder and arterial oxygen saturation (SaO_2) through a Hewlett-Packard ear oximeter during the night in eight "blue bloaters", and six smokers with ischaemic heart disease.

In seven "blue boaters" the mean basal nocturnal SaO_2 fell to below 80% and all developed multiple atrial and ventricular premature contractions and a high resting heart rate; six patients had a prolonged QTc, and three developed ST-T changes. Oxygen therapy (24%) increased their basal SaO_2, reduced their ectopic activity, reduced the resting heart rate ($p<0{\cdot}01$), abolished ST-T changes, significantly ($p<0{\cdot}001$) reduced the amplitude of R and S waves, and shortened the QTc in four non-smokers. In heavy smokers the estimated mean basal SaO_2 (carboxyhaemoglobinaemia and oximeter reading) during the night fell to 84%, the resting heart rate was higher than normal subjects and they had ectopic activity as well as a prolonged QTc. Oxygen treatment did not improve the electrocardiographic changes either in this group or in smokers with chronic obstructive airways disease. A long acting beta-adrenoreceptor blocking agent (nadolol) reduced ectopic activity in smokers but did not influence other electrocardiographic changes. These studies suggest that sustained hypoxaemia contributes to myocardial dysfunction in "blue bloaters" and in heavy smokers. Oxygen treatment is beneficial in the former but ineffective in the latter because of carboxyhaemoglobinaemia.

Usefulness of psychological questionnaires in evaluation of patients with mitral valve prolapse syndrome

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Psychological disturbances are commonly recognised in the mitral valve prolapse syndrome. To evaluate the frequency and types of psychological disturbances encountered, 105 patients with echocardiographically confirmed mitral valve prolapse syndrome and 95 control subjects were asked to complete psychological questionnaires—the hysteroid-obsessive questionnaire (HOQ), the Eysenck personality inventory, forms A and B (EPQA, EPQB), and The Middlesex Hospital questionnaire (MHQ).

On average, patients with mitral valve prolapse syndrome were neither less extrovert nor truthful than controls ($p>0{\cdot}05$) and did not show altered hysteroid traits (HOQ, $p>0{\cdot}05$; MHQ "H" score $p>0{\cdot}05$).

Free-floating anxiety scores were much higher in patients with mitral valve prolapse syndrome than in controls (MHQ "A" $p<0{\cdot}001$, EPQ "N" (A+B), $p<0{\cdot}001$). Obsessoid scores were also much higher in patients with mitral valve prolapse syndrome ($p<0{\cdot}001$), as were depressive and paranoid scores. Somatisation, the tendency to localise psychological disturbances to body sites, was much more obvious in patients with mitral valve prolapse syndrome than in controls ($p<0{\cdot}0001$).

Patients with mitral valve prolapse syndrome, therefore, showed very abnormal psychological questionnaire scores, suggesting that mitral valve prolapse syndrome is closely related to Da Costa's syndrome, the soldier's heart syndrome, the effort syndrome, and neurocirculatory asthenia.

Our results indicate that anxiety and the other psychological disturbances are prominent features of the mitral valve prolapse syndrome and probably influence the symtomatology of the condition. Using the tests listed, the pattern of abnormalities in the psychological scores appears sufficiently characteristic to help confirm the diagnosis in suspected cases. We are currently comparing the scores of patients with the mitral valve prolapse syndrome with those from patients with longstanding symptoms resulting from other conditions, such as ischaemic heart disease.

Pharmacological mapping in rabbit heart

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A method for studying the relative effects of drugs in various parts of the rabbit heart shows that different regions exhibit quantitatively different responses to the same drug. Intracellular potentials were recorded from the sinoatrial node and atrial muscle, and from the His bundle, terminal Purkinje, and ventricular cells, before and after exposure to three drugs, Melperone, UP 339.01, and alinidine. All these compounds produce a bradycardia in isolated hearts, but the sinoatrial node records indicate that they do so by entirely different mechanisms.

In papillary muscle UP depressed the maximum rate of depolarisation but only by half as much as observed in the atrium at comparable concentrations. In atrial tissue APD$_{90}$ (but not APD$_{20}$ or APD$_{50}$) was slightly increased, whereas in ventricular muscle APD (action potential duration) was uniformly prolonged even by the lowest concentrations. Even within the ventricular conduction system Melperone had quantitatively different effects at proximal and distal sites. Melperone (10·7μM) prolonged APD$_{90}$ by 54% in the bundle of His and by 40% in ventricular muscle. In contrast, in terminal Purkinje cells, APD$_{90}$ was increased by only 15·6%.

It was concluded than an antiarrhythmic agent cannot be fully characterised unless a "pharmacological map" presents relative quantitative effects on all parts of the heart.

Platelets and coronary artery disease—clinical and experimental study

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Platelet counts, aggregates, and in vitro aggregation were measured in arterial, coronary sinus, and peripheral venous blood in patients with and without coronary artery disease. Platelet counts were unaltered. Aggregates were present in coronary sinus blood during spontaneous or ergometrine-induced, but not during pacing-induced angina. Aggregates were high in systemic blood only from patients with unstable angina. In patients with coronary artery disease, in vitro aggregation was increased in coronary sinus blood at rest but reduced during pacing-induced ischaemia. Peripheral venous levels of beta-thromboglobulin were raised in patients with angina and myocardial infarction.

Myocardial hypoxia in the isolated perfused rabbit heart resulted in the release of an antiaggregatory substance into the effluent perfusate. This release was not prevented by the addition of cyclo-oxygenase inhibitors, eicosatetraynoic acid or quinacrine to the perfusate. No increase in the effluent concentration of 6-keto-prostaglandin F$_{1\alpha}$ was evident during these hypoxic periods.

These findings suggest that platelet aggregability is increased on transit through stenotic coronary arteries but reduced during ischaemia by the release of an antiaggregatory substance. During severe proximal constriction sufficient to cause angina at rest when there is presumably greater turbulence and platelet damage at the site of stenosis, the ischaemia-induced antiaggregatory effect is insufficient to prevent aggregate formation.

Role of cardiac beta-receptors in development of adaptive cardiac hypertrophy

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Experiments have been carried out in rats to test the hypothesis that a substance liberated from the terminals of cardiac sympathetic nerves is the factor that induces compensatory cardiac hypertrophy. It was found that prior chemical sympathectomy (high dose guanethidine treatment) completely prevented the adaptive cardiac hypertrophy caused by chronic exercise. Isoprenaline-induced cardiac hypertrophy was not affected by chemical sympathectomy, suggesting that it is the action of noradrenaline on cardiac beta-adrenoceptors which induces cardiac hypertrophy. Further evidence that noradrenaline is the trigger factor is that the compensatory hypertrophy that follows aortic coarctation was reduced by 65% by oral treatment with propranolol, through an action which was independent of any reduction in cardiac work.

It is proposed that noradrenaline secreted from cardiac sympathetic nerves is the trigger that initiates adaptive cardiac hypertrophy; that this action of noradrenaline is mediated by beta-adrenoceptors; and that in clinical medicine treatments that interfere with neurotransmission in cardiac sympathetic nerves may prevent cardiac hypertrophy from becoming excessive and interfering with myocardial function.

Regional variation of left ventricular transit time in normal ventricles and those with abnormal contraction

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This study demonstrates regional differences in the time taken for a radionuclide bolus to pass through the left ventricle.

A combination of left ventricular ejection fraction estimation and a relatively new radionuclide technique which can be used to detect regional ventricular disease—phase imaging—was used to divide 33 subjects with chest pain into 13 normal and 20 with abnormal ventricles. The time taken for an intravenously injected radionuclide bolus to appear and to pass through septal, apical, and lateral left ventricular segments was measured in all subjects.

In the normals, appearance times were larger in the apical (8 ± 1 cardiac cycles) than septal (7 ± 1) and lateral (7 ± 1) segments and transit times prolonged (apical 36 ± 6, septal 24 ± 5, and lateral 26 ± 5). Compared with the normals, those with abnormal ventricles had longer appearance and transit times but the differences between the apical and the two basal regions persisted. These subjects also manifested differences between septal and lateral transit times (mean difference 5 ± 5) which had not been present in the normals (mean difference 1 ± 1).

The left ventricle is a poor mixing chamber. Pools of relative stasis are found at the apex in both normal and abnormal ventricles and, in the latter, in the body of the chamber.

National survey of deaths from aortic valve disease

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The circumstances of deaths from aortic valve disease were investigated by obtaining copies of all death certificates issued with that diagnosis in subjects aged below 70 who died in England and Wales in 1979. A questionnaire was sent to the relevant general practitioners, hospital doctors, and coroners asking for details of the previous degree of recognition of the disease, the medical care received, and the suddenness of death.

There were 261 cases of mixed aortic and mitral valve disease studied and 923 cases of pure aortic valve disease and the results of the survey showed distinct differences between them. In the mixed valve disease category 80% were on treatment; 5% were fully fit a month before death and in 4% the diagnosis was made for the first time at necropsy. By contrast, only 57% of the pure aortic valve disease cases were on treatment whereas 17% were fully fit one month before death and in 22% the diagnosis was first made at necropsy. Of the mixed valve disease cases, 72% had been diagnosed more than five years versus only 37% of the pure aortic valve disease cases. More than a third of the mixed cases had had surgery and 18% of those with aortic valve disease; in half of all these cases the surgery was within one month of death.

Despite the advances in treatment the diagnosis of aortic valve disease is still frequently missed.

Late results of mitral valve replacement using unstented antibiotic sterilised aortic homografts

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Three hundred and seventy-nine patients who underwent mitral valve replacement using unstented antibiotic sterilised aortic homografts, have been followed up for two to 10 years (mean 73 months). Patients requiring additional aortic valve replacement were excluded. The commonest cause was rheumatic heart disease (320 patients), followed by floppy valve syndrome (42 patients). There were 37 early deaths (9·8%) and 92 late deaths (24%). The actuarial survival of operative survivors was 83% at three years, 75% at five years, and 61% at nine years. Technical valve failure occurred in six patients (1·6%), infective endocarditis in 19 (5%), and degeneration of the valve in 30 (8%). The cumulative probability of freedom from endocarditis was 96% at three years, 94% at five years, and 91·4% at nine years, while that of freedom from valve degeneration was 99% at three years, 97% at five years, and 67% at nine years. There were no early embolic episodes, but late embolism occurred in five patients (1·3%).

It is concluded that homograft replacement of the mitral valve gives satisfactory results for up to 10 years. There is, however, a continuing incidence of endocarditis, and a progressive increase in the rate of valve degeneration after the sixth year.

Surgical outcome in post-infarction ventricular spetal defect

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The cases of 50 consecutive patients treated for post-infarction ventricular septal defect were reviewed. Cardiac catheterisation was carried out in all patients and surgical repair was undertaken in 32 patients.

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The main factors affecting surgical outcome were the site of infarction and the extent of right ventricular damage.

Anterior myocardial infarction carried a better hospital survival rate than inferior infarction (67% and 31%, respectively). Right ventricular free wall infarction, present in 39% of anterior infarctions and 69% of inferior infarctions, carried a poor prognosis. Of patients with good right ventricular contraction, 80% (12/15) survived the operation compared with only 24% (4/17) of patients with poor right ventricular contraction.

Operation within 24 hours to 14 days of infarction carried a survival rate of 50% (7/14), similar to that in patients operated after two weeks of infarction (9/18).

The 18 patients who did not have an operation either died suddenly before scheduled operation or were considered poor surgical risks. Of these, 12 patients died within one week of infarction, five patients survived between two weeks and three months, and one patient with good right ventricular contraction and anterior infarction refused operation and survived four and a half years.

We conclude that early surgical repair should be considered in all patients with post-infarction ventricular septal defect and early operation in patients with good right ventricular contraction carries an excellent prognosis.

Heart and lung transplantation

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As part of our heart transplantation programme we have begun clinical trials of combined heart and bilateral lung transplantation. Between 9 March and 28 July 1981 three patients underwent heart-lung transplantation. Indications were: primary pulmonary hypertension (45-year-old woman); congenital heart disease with Eisenmenger syndrome (30-year-old man and 28-year-old woman). Operative technique included anastomosis of trachea just above the carina, ascending aorta, and right atrium. Graft ischaemic times were 55, 62, and 75 minutes. Ventilatory support was removed within 30 hours postoperatively in two patients. Case 3 (28-year-old woman with two previous cardiac operations) had extensive perioperative haemorrhage, hepatic and renal failure, and died four days after operation.

Immunosuppression is provided by Cyclosporin-A and low dose prednisone, supplemented perioperatively with azathioprine, rabbit antithymocyte globulin, and methylprednisolone. Rejection was diagnosed by serial endomyocardial biopsy on two occasions in one patient; pulse therapy of methylprednisolone and rabbit antithymocytic globulin produced resolution. No significant infection or tracheal complications have occurred. Two patients continue well, five months and three months after operation. Our experience suggests the feasibility of heart-lung transplantation for endstage cardiopulmonary disease.

Value of ST segment/heart rate relation during exercise as index of severity of coronary artery disease

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Recently, in a group of 64 patients with angina pectoris admitted for coronary arteriography,[1] it was suggested that the maximal rate of progression of ST segment depression relative to increases in heart rate during exercise (maximal ST/HR slope) may be used reliably to predict the presence and severity of coronary artery disease.

The ability of the test to predict has now been examined in 160 patients with angina; the patients included 41 patients on beta-blocker treatment and nine with valve disease, hypertrophic cardiomyopathy, or left bundle-branch block. In 129 patients there was significant coronary artery disease ($>75\%$ luminal narrowing of at least one major artery). The maximal ST/HR slope averaged 18·1mm beat per min per 10^3 (range 13 to 21) in 37 patients with single-vessel disease, 43·8 mm beat per min per 10^3 (range 32 to 59) in 54 patients with double-vessel disease, and 85·9 mm beat per min per 10^3 (range 69 to 137) in 38 patients with triple-vessel disease. These values are significantly different from each other ($p < 0{\cdot}0005$, unpaired t test). In 31 patients without significant coronary artery disease, the maximal ST/HR slope averaged 8·8 mm beat per min per 10^3 (range 3 to 11) and was significantly different from that in any of the three groups with significant coronary artery disease ($p < 0{\cdot}0005$). All these results are precisely within the ranges previously described as predicting insignificant, one, two, or three vessel disease.

It is concluded that the maximal ST/HR slope accurately predicts, without false results, the presence and severity of coronary artery disease in individual patients with angina pectoris.

Reference

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Factors affecting use of R wave changes in detection of myocardial ischaemia

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Analysis of R wave amplitude change has been advocated for the improved diagnosis of coronary disease. We studied three groups of patients (off treatment) to assess the diagnostic value of this measurement, its reproducibility, and relation to left ventricular volume. Two hundred patients undergoing coronary angiography (group A) had 16 lead praecordial exercise mapping. Ten patients with proven coronary disease and exercise ST depression underwent three identical exercise tests within six weeks. In a further 10 patients (group C), R wave amplitude and left ventricular volume were continuously assessed during provocative tests for ischaemia, using a technetium-99M labelled blood pool and scintillation probe. In group A, 154 patients had coronary disease: the R wave increased or remained unchanged in 61 patients and fell in 93 (sensitivity 40%). R wave increased or did not alter in 30 of 46 patients without coronary disease (specificity 35%). The sensitivity and specificity for ST depression were 79% and 89%, respectively. In group B, the R wave changes during serial tests were consistent in each individual, but inconsistent for the group. Similarly in group C the relation between R wave and left ventricular volume was reproducible in each patient, but different between patients consistently related to ST depression or left ventricular volume changes. Praecordial R wave changes are not consistently related to ST depression or left ventricular volume. In addition, they are too variable to have diagnostic value in patients with coronary disease.

Ambulatory ST segment monitoring with frequency modulated system—facts, artefacts, and fallacies

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Using an Oxford Medilog Mark 2 frequency modulated recorder we obtained 1200 tapes during ambulant daily activity on 360 patients with suspected or confirmed ischaemic heart disease. Scrupulous care was taken to apply electrodes properly and anchor cables and recorder securely. The tapes were analysed using newly-developed computer techniques and analogue write-outs. Satisfactory tapes for accurate ST segment analysis were obtained in 89%. Recorder malfunction and internal cable fracture accounted for the majority of failures and the rest were the result of electrode problems. Common artefacts were DC shift, noisy signals caused by recorder playback head misalignment, and noisy baseline. Clock failure was seen in about 10% of tapes and inaccurate time signals in another 15%. A curious ST segment elevation resembling Prinzmetal's angina was seen during clock failure in three tapes. Fastidious care and maintenance of recorders with a high awareness for artefact identification and elimination were essential for successful and accurate monitoring of ambulatory ST segment changes. Digital analysis or analogue write-outs were developed for quantification and replaced visual analysis for accurate results. All results were compared with computer assisted exercise testing using identical leads and methods of analysis. Ambulatory ST monitoring was identical to exercise testing in 80% of patients, 20% disclosed additional information unavailable during exercise testing. Those changes included ST segment elevation, ST depression associated with ST elevation, multiple episodes of ST depression unassociated with heart rate increase, and dissociation between severity of changes during exercise testing and ambulatory monitoring. These findings firmly established ambulatory ST segment monitoring as a valuable additional investigation to exercise testing.

Is computer analysis of exercise testing worth while?

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Computer assisted exercise testing provides accurate and objective assessment of electrocardiographic changes during exercise and facilitates the quantification of numerous derivatives of these changes. These systems are, however, very expensive. In order to evaluate the merits and limitations of such a system we have studied a group of 90 patients referred with chest pain who subsequently underwent coronary arteriography. Seventy variables obtained from each patient during exercise testing were submitted to discriminant analysis. Using only six of these variables it was possible to obtain a positive predictive value of 85%.

By far the most important variable was the ST slope index [(ST max − ST rest) + ST slope]. Electrocardiographic changes observed at peak exercise changed very rapidly during the period immediately after exercise clearly showing that the electrocardiogram must be monitored *during* and not after exercise.

We feel that, because of the ability to monitor variables such as ST segment slope during exercise with accuracy and objectively, exercise laboratories should include a computerised analysis system.

Fully implantable automatic scanning pacemaker for tachycardia termination

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A new fully implantable scanning pacemaker, requiring no external control unit, has been implanted in 13 patients. On detection of tachycardia an extrastimulus is generated at a preprogrammed initial coupling interval. Failure to terminate tachycardia leads to a reduction in this coupling interval by 6 ms, a process that may, if necessary, be repeated up to a maximum of 15 times. A second extrastimulus may also be selected at a programmable but static coupling interval from the first. A memory function is incorporated to reuse successful timings immediately should tachycardia recur.

Six of the patients had intra-atrioventricular nodal re-entrant tachycardia, and seven had atrioventricular re-entrant tachycardia. Tachycardia cycle length varied from 275 to 430 (mean 332) ms and patients suffered 0·25 to 450 (mean 42) attacks per month. Ten were considered to have failed conventional medical treatment (3 to 7, mean 5·3 drugs), while three elected for pacing early in their management. Six had previously received patient-activated pacemakers. The right ventricle was paced in 10 patients (three single, seven double extrastimuli), and the right atrium was paced in three (double stimuli). Pacing was fully effective both lying and standing in all patients, though two required beta-blockade to allow termination in the upright posture. Termination usually occurs before a sustained tachycardia has been appreciated by the patient, though one patient had a sustained tachycardia requiring reprogramming of the pacemaker.

Analysis of persistent symptoms in patients paced for carotid sinus syncope

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Seventy syncopal patients with the hypersensitive carotid sinus syndrome have been paced. All patients had reproducible hypersensitive carotid sinus reflexes (asystole exceeding three seconds), with symptoms which were abolished by temporary ventricular pacing. Twelve patients had persistent symptoms despite adequate ventricular pacing (group 1). They were compared with 14 asymptomatic carotid sinus syndrome patients (group 2) and 12 controls (group 3).

Intra-arterial pressure recording was used to determine the maximum hypotension occurring after atrioventricular sequential pacing and carotid sinus massage (vasodepressor response), after the introduction of ventricular pacing (pacemaker effect), and after simultaneous carotid sinus massage and introduction of ventricular pacing (combined effect). Group 1 patients (persistent symptoms) had the greatest responses: vasodepressor 52 mmHg, pacemaker effect 52 mmHg, and combined effect 76 mmHg, with the latter reproducing symptoms in all. Group 2 patients had a smaller vasodepressor response: 29 mmHg ($p < 0{\cdot}001$), pacemaker effect 42 mmHg ($p < 0{\cdot}01$), and combined effect of 50 mmHg ($p < 0{\cdot}01$). Group 3 patients had an insignificant vasodepressor response and a pacemaker effect equivalent to group 2 (35 mmHg).

Atrioventricular sequential pacing was shown to eliminate the pacemaker effect and abolish persistent symptoms during carotid sinus massage and is considered to be the treatment of choice for carotid sinus syndrome patients with both cardioinhibitory and significant vasodepressor responses.

The Birmingham trial of pacing in intraventricular block after acute myocardial infarction

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Since 1976, 41 patients with intraventricular conduction block who survived 14 days after acute myocardial infarction have been randomised to permanent pacing or control groups. These patients represented 2·4% of acute infarct admissions to coronary care. Patients had right bundle-branch block alone or combined with left anterior or posterior hemiblock, or left posterior hemiblock alone. Control and pacing groups have been well matched for age, sex, previous infarction, maximum enzyme rise, Norris index, and presence of heart failure. Differences in survival have not been statistically significant. Fewer patients with the uniformly fatal combination of right bundle-branch block and left posterior hemiblock were randomised to control (two patients) than pacing (six patients). This difference may explain the tendency (not significant) towards more favourable survival in control patients (82% and 71% at one and two years, respectively) compared with paced patients (67% and 63%, respectively). HV conduction times have not predicted outcome. A deterioration in intracardiac conduction during follow-up has been observed in only one patient whereas eight showed improvement. These recruitment and survival rates are pertinent to the recently established UK multicentre trial of pacing after acute infarction; separate stratification according to site of conduction block may be advisable.

Continuous recording of coronary sinus oxygen saturation during pacing test as method for detection of coronary artery disease in patients with chest pain

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Blood flow to the normal heart increases in proportion to cardiac work so that sufficient oxygen is supplied to the myocardium and excess metabolites are removed. We have recorded continuously coronary sinus oxygen saturation in 14 patients being investigated for chest pain. Oxygen saturation was measured with a catheter tip fibreoptic electrode (Oximetrix, California). The instrument gives stable and reliable measurements of mixed venous oxygen in the pulmonary artery of man for periods in excess of 48 hours. After the catheter was placed in the coronary sinus an atrial and ventricular pacing test were performed. Heart rate was increased by 10 beats/min each minute. Systolic and end-diastolic ventricular pressure and a 12 lead electrocardiogram were recorded during and immediately after each increment in heart rate. Coronary angiography was performed subsequently. Two of the 14 patients had normal coronary arteries. In normal hearts or in the absence of any other evidence indicating myocardial ischaemia, an increment of heart rate increased oxygen extraction, but after 20 seconds the coronary sinus oxygen saturation returned to control values, the expected consequence of vasodilatation. In patients with fixed coronary stenoses the increased extraction persisted, increased with increasing heart rate, and preceded other indicators of myocardial ischaemia. Adaptation of coronary blood flow to altered cardiac work is rapid in man. Oxygen extraction from coronary blood can be increased by up to 30%. A persistent increase in oxygen extraction appears to be a good indicator of coronary artery disease.

Comparison of peak exercise and immediate post exercise imaging in detection of regional wall motion abnormalities in patients with coronary artery disease

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Radionuclide angiography is valuable for the detection of exercise-induced abnormalities of regional wall motion. The timing of exercise imaging is a major procedural variable in the conduct of exercise radionuclide angiography. In this study (A) 10 patients with normal coronary arteries of less than 50% stenoses of the coronaries and (B) 17 patients with significant coronary disease were imaged upright at rest, at peak exercise, and immediately after exercise by first pass radionuclide angiography. Regional wall motion was evaluated from count-based regional ejection images, a regional ejection fraction of less than 50% for anterior, apical, and inferior zones being abnormal. Images were interpreted independently and blind by four observers. The results are expressed as the number of patients with an abnormal regional ejection image, with the total number of abnormal zones in parentheses (Table).

	Rest	*Peak exercise*	*Immediately after exercise*
Group A	0 (0)	4 (8)	1 (1)
Group B	8 (16)	17 (44)	12 (26)

Results show that sensitivity, specificity, and predictive value for the detection of coronary artery disease by an abnormal regional ejection image were 100%, 60%, and 81% at peak exercise, and 70%, 90%, and 92% immediately after exercise.

In conclusion (1) some patients with less than 50% stenoses may show abnormal wall motion at peak exercise though rarely immediately after exercise; (2) abnormal regional wall motion at peak exercise is therefore sensitive but not specific for significant coronary artery disease; (3) if imaging is performed only at rest and immediately after exercise, the sensitivity for significant coronary artery disease will be reduced though abnormal regional wall motion immediately after exercise has high specificity and predictive value.

Comparison of exercise ST-isopotential surface mapping and ^{201}Tl scintigraphy in detecting extent of coronary disease

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T D V Lawrie
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Exercise ST-isopotential surface mapping and exercise ^{201}Tl scintigraphy have been advocated as sensitive non-invasive investigations in the diagnosis of coronary disease. To test the relative merit of these techniques in determining the extent of vessel disease, both sets of data were obtained in 30 male patients with arteriographic evidence of obstructive coronary disease, but without previous myocardial infarction. ^{201}Tl scans were interpreted using a semiquantitative method of regional analysis. ST-isopotential surface maps were constructed from a 16 electrode praecordial matrix using a PDP8 computer. The location of scintigraphic defects and the praecordial projection of ST abnormality ($\geqslant -0{\cdot}1$ mV) were related to the arteriographic distribution of coronary disease. Scintigraphy was abnormal in 25 and ST maps abnormal in 28 of the 30 patients. Of the 63 vessels diseased (left anterior descending, LAD 26; left circumflex, LCX 16; right coronary artery, RCA 21) scintigraphy detected 41 (LAD 15; LCX 9; RCA 17) and ST mapping detected 56 ($p<0{\cdot}01$) (LAD 23; LCX 13; RCA 20). Extensive praecordial ST abnormality identified 11 of the 13 patients with triple vessel disease, while scintigraphy predicted triple vessel disease in four of those 13 patients ($p<0{\cdot}02$). Thus exercise ^{201}Tl scintigraphy and exercise ST mapping identified the presence of disease with similar frequency, but ST mapping provided a more accurate guide to the extent of coronary disease.

Can ventricular extrasystoles enhance localisation of exercise-induced ischaemia

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Previous work from this department has shown that the standard 12 lead electrocardiogram can localise the exact site of origin of ventricular extrasystoles. An atlas of extrasystolic appearances from individual ventricular sites has been drawn. In view of the relation between myocardial ischaemia and ventricular arrhythmias we were interested in their comparative anatomy.

Two hundred and ten patients underwent maximal exercise testing on a bicycle ergometer, before thallium scintigraphy. All 12 leads of the electrocardiogram were recorded simultaneously at rest, immediately after exercise, and then for several minutes afterwards. Thallium-201 was injected intravenously at maximal exercise and the patients subsequently scanned.

Twenty-nine of the 210 patients had ventricular arrhythmias on exercise. Nineteen of these patients had otherwise negative exercise tests with no ST or T wave changes and, of these, 17 had coronary artery disease on scintigraphy. One patient had hypertrophic cardiomyopathy and the other congestive cardiomyopathy. Localisation of the arrhythmias was possible in every patient. Those with reversible posterior (circumflex) defects had right bundle-branch block ectopics with a limb lead QRS vector of −60° to −150°. Reversible inferior defects showed extrasystoles with left bundle-branch block and a superior axis. Extrasystoles of septal origin could present with either right or left bundle-branch block and an inferior axis from the upper septum or superior axis from the lower septum. The patient with hypertrophic cardiomyopathy had ventricular extrasystoles of left septal origin.

Thus in this series analysis of ventricular extrasystoles in otherwise negative exercise electrocardiograms was useful. The appearance of the extrasystoles in all 12 leads can localise its site of origin and this having been ascertained it may be correlated with the area of ischaemia. This may give valuable information about the extent of disease in the supplying coronary artery.

Investigation into smoking-induced tachycardia and effect of beta-blockade on exercise-induced tachycardia and oxygen consumption in heavy smokers

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Smoking is a well-known risk factor in ischaemic heart disease but the extent of its interference with exercise testing for diagnosis, and with beta-blockade for treatment is not well established. We studied heart rate and oxygen consumption (VO_2) at maximal exercise load with and without beta-blockade in five smokers (>20 cigs/day) and seven non-smokers. After a training period of three weeks all subjects were randomised to receive, intravenously, either placebo or propranolol (0·25 mg/kg).

The smoker group had a mean resting heart rate (75 ± 3 bpm ± SD) significantly higher ($p < 0{\cdot}01$) than non-smokers (64 ± 5 bpm). At the maximal exercise load of 5400 kpm, smokers had a mean heart rate of 176 ± 14 as compared with 156 ± 6 in non-smokers ($p < 0{\cdot}02$), while VO_2 was not significantly different at 2·90 ± 0·6 l/min as compared with 2·76 ± 0·05 l/min. Propranolol reduced exercise-induced tachycardia in both groups but the heart rate for the same work load was significantly ($p < 0{\cdot}01$) higher in smokers than in non-smokers (136 ± 3 Vs 125 ± 8 bpm). During the resting period of 10 minutes after exercise, the heart rate in non-smokers settled to a mean of 78 ± 9 as compared with 105 ± 11 bpm in smokers while VO_2 showed a comparable fall in both groups. Our studies show that this work-heart rate disproportion and the inadequate suppression of heart rate by propranolol is a result of decreased oxygen carrying capacity (carboxyhaemoglobinaemia) in smokers and exercise tests or treatment with beta-adrenoreceptor blocking drugs must take account of this.

Release of thromboxane during atrial pacing and haemodynamic and metabolic effects of inhibition by dazoxiben

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Thromboxane A_2 is a powerful vasoconstrictor, which, it has been suggested, may contribute to both spontaneous and exercise-induced myocardial ischaemia. The release of thromboxane B_2 (the stable derivative) into the coronary and systemic circulations during atrial pacing stress was measured in 10 patients with angiographically proven coronary artery disease. The influence of dazoxiben (a new selective inhibitor of thromboxane synthetase) on this release has been studied.

Mean atrial thromboxane B_2 rose during control pacing from 173·2 pg/ml to 529·8 pg/ml, but after an oral dose of dazoxiben (200 mg) was unchanged (264 and 206 pg/ml, respectively). Raised coronary sinus levels were recorded before, but not during, myocardial ischaemia, whereas the rise in the arterial levels occurred at, or after, the onset of ischaemia.

Associated with the inhibition of thromboxane release, dazoxiben had no significant effect on cardiac output, heart rate, pacing time to angina, or systemic and pulmonary arterial pressures. Coronary sinus blood flow increased from 205 ml/min to 241 ml/min during pacing and mean lactate production fell from 23·9 μmol/min to 1·13 μmol/min.

The release pattern of thromboxane B_2 suggests two sources, that is coronary and pulmonary circulations. Dazoxiben inhibits this release and its evaluation in patients with angina in a formal controlled trial should allow further assessment of its therapeutic importance.

Cardiovascular effects of selective thromboxane synthetase inhibitor in patients with coronary heart disease

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Thromboxane A_2 is a potent vasoconstrictor released by platelets which can cause further aggregation of circulating platelets. It has been speculated that thromboxane may have an important role in coronary heart disease, and particularly in the patient with coronary artery spasm. The effects of UK 37248, a selective thromboxane synthetase inhibitor were studied in 20 patients with coronary heart disease. Coronary and systemic haemodynamics were studied in these patients and simultaneous blood samples from aorta and coronary sinus for measurement of thromboxane B_2 were obtained in all patients before and one hour after the oral administration of 100 mg of UK 37248. There were no significant haemodynamic changes—heart rate being 69±5 and 66±3 beats/min, blood pressure 100±2 and 96±5 mmHg, cardiac output 5·4±0·4 and 5·3±0·4 l/min, and MVO_2 was unchanged at 16·4±2 and 16·1±2 ml/min. At rest the drug reduced coronary sinus thromboxane B_2 from 105±47 to 50±3 pg/ml and reduced arterial thromboxane B_2 from 277±130 to 52±2 pg/ml ($p < 0·02$). Atrial pacing time to angina increased from 4·3±0·9 to 5·5±0·9 min ($p < 0·001$) and coronary sinus thromboxane B_2 fell from 153±50 to 56±4 pg/ml and arterial thromboxane B_2 fell from 168±37 to 50±3 pg/ml ($p < 0·025$). Preliminary results in seven patients with unstable angina have confirmed these significant reductions in arterial and coronary sinus thromboxane levels. It is concluded that UK 37248 has no significant haemodynamic effect and produces significant reductions in both arterial and coronary sinus thromboxane B_2 in patients with both stable and unstable angina.

Effects of platelet inhibition on transient episodes of myocardial ischaemia

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We have examined the effects of ticlopidine, an inhibitor of platelet aggregation, in studies involving both dogs and man. Ten open-chest dogs were evaluated for five hours after an oral dose. There were no detectable haemodynamic effects and no changes in the electrocardiogram, myocardial oxygen consumption, coronary flow, or resistance. Ten patients with daily angina underwent three single-blind treatments assessed with four days ambulatory monitoring: (a) placebo (two weeks), (b) ticlopidine (four weeks), (c) placebo (two weeks). At the end of the first placebo period there were 8·3±5·7 (mean±standard deviation) episodes of angina and 20·9±12·6 episodes of ST depression. After four weeks ticlopidine there were 4·8±3·2 episodes of angina and 8·1±5·8 episodes of ST depression. This difference was the result of a significant reduction in angina (placebo 3·7±2·1, active 0·7±0·6) and ST depression (placebo 9·6±7·4, active 1·4±1·3) that occurred without increase in heart rate ($p < 0·01$). Both angina and number of episodes of ST depression were similar in the two placebo periods ($p > 0·05$).

Thus, ticlopidine, an inhibitor of platelet aggregation can reduce the frequency of angina and electrocardiographic evidence of myocardial ischaemia that occurs without increase in heart rate. This may affect future treatment and raises pathophysiological questions in angina pectoris.

Effects of menopause on clotting factors and ischaemic heart disease

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The incidence of ischaemic heart disease increases after the menopause. The increase is not as abrupt as is often thought, but the Framingham study shows incidence rates two or three times higher in post- than premenopausal women of the same age. Data on 835 white women in the Northwick Park Heart Study have been used to identify variables that may be involved in the pathogenesis of ischaemic heart disease and that differ between pre- and postmenopausal women. Mean levels of cholesterol, factor VII, fibrinogen, and antithrombin III were significantly higher in postmenopausal women. There was no difference in blood pressure. The cholesterol finding has been reported before. The Northwick Park Heart Study has established that high factor VII and fibrinogen levels in men are each independently associated with an increased risk of death from ischaemic heart disease. The factor VII and fibrinogen results by menopausal status strengthen the evidence that high levels are of pathogenetic significance. In the case of fibrinogen, the increase with age after the menopause is significantly greater than before. The higher antithrombin III level in postmenopausal women may be a protective adaptation to increases in variables tending to promote thrombosis.

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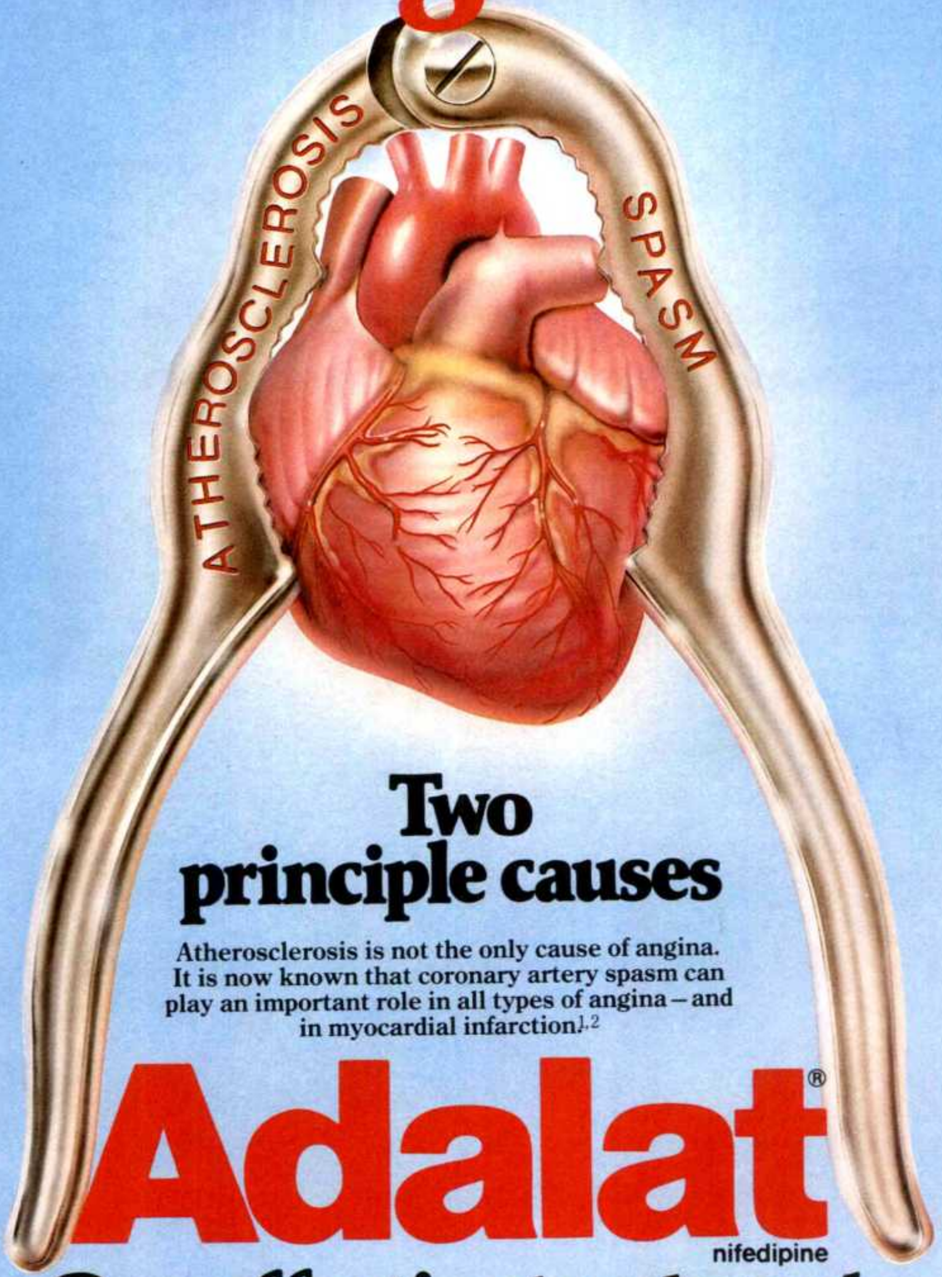

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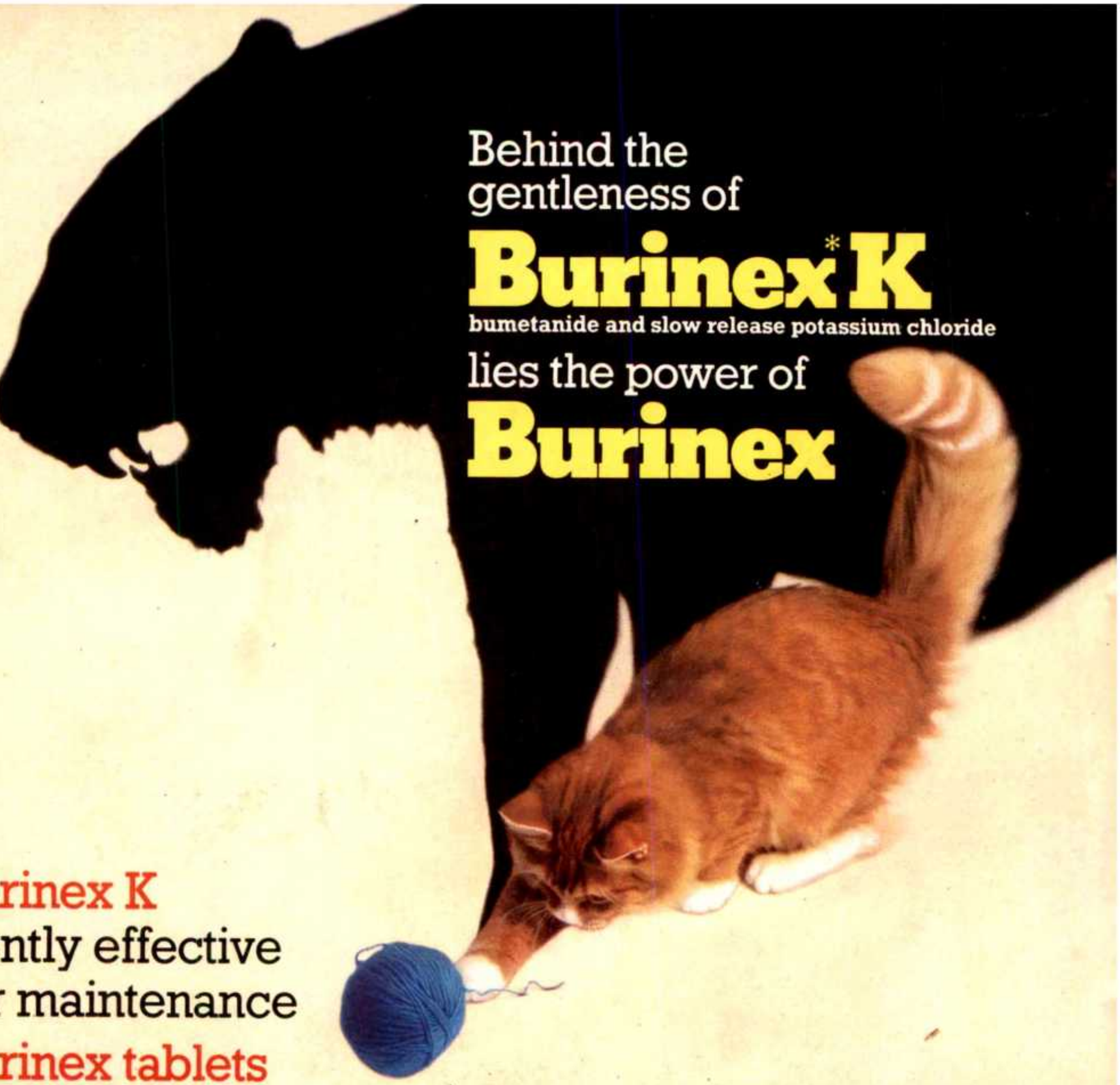

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Papers relating to the heart and circulation should be sent to the Editor, *British Heart Journal*, BMA House, Tavistock Square, London WC1H 9JR. *A stamped addressed* envelope or an international reply coupon *must* accompany the manuscript if acknowledgment of receipt is desired. Submission of a manuscript will be held to imply that the work is original, that it has not been published elsewhere, and that if accepted it will not be published elsewhere in whole or in part without the Editor's permission.

All contributions (including correspondence) should be typed on one side of the sheet only, in double spacing with margins of at least 4 cm. A second copy of the MS, tables, and figures should be sent but will not be returned to the author even if the paper is rejected. Papers should be concise and contain an informative summary, embodying methods, results, and conclusions. Titles of papers should be brief and should be typed on a separate sheet of paper together with authors' names, institution where the work was done, and a short title for the running heads. The title page should list: (i) authors' present addresses if these have changed, and (ii) name and address of the author to whom correspondence and proofs should be sent. If unusual abbreviations are used to avoid frequent repetition of complex designations then these must be clearly identified. Suitable acknowledgment of financial support or assistance may be made but should not be extended to include those whose contribution consisted only of the performance of the normal duties for which they were employed.

SI units Units in which the authors' work was measured should be cited first followed by either SI units or traditional units. This does not apply to Tables, but here a conversion factor should be added as a footnote.

Case reports are intended to convey only the essential facts of a case, and discussion and bibliography should be kept to a minimum. They should have no more than three authors, should not exceed 1500 words, and should contain no more than two Figures.

Tables (see also SI units above) must be typed on separate sheets and not in the text. They should be numbered with Arabic numerals and should have a title. Column headings must be clear without lengthy explanatory footnotes.

Illustrations should be identified on the back with Figure number in Arabic numerals and name of author. Legends should be typed on a separate sheet of paper. Figures should be on glossy paper and unmounted unless several are grouped together as in montage. Lettering to be inserted should be indicated lightly in pencil on a transparent overlay. *Diagram, charts*, and *line drawings* should be drawn in indian ink. Only black-and-white *electrocardiograms* make satisfactory blocks, and photographs should be sent rather than original. If several electrocardiograms are grouped in a single Figure, only a few complexes should be shown, and the width should not exceed 14 cm unless a reduction in scale is feasible. *Radiographic prints* (see Editorial, vol 35,p 1101, 1975) should be submitted unmounted as facsimile (negative) glossy prints of at least half-plate size, with as long a tonal range as possible. Include only area under discussion. Letraset arrows, transparent overlays, and explanatory line drawings should be used when necessary. Identify on back with author's name, "TOP", and figure number written in felt tip pen.

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(1) *Standard journal article*—(List all authors when six or less; when seven or more, list only first three and add *et al.*):
   Walmsley R. Anatomy of left ventricular outflow tract. *Br Heart J* 1979; **41**: 263–7.

(2) *Books and other monographs:*
   Macartney FJ, Partridge JB, Shinebourne EA, Tynan MJ, Anderson RH. Identification of atrial situs. In: Anderson RH, Shinebourne EA, eds. *Paediatric cardiology 1977*. Edinburgh, London: Churchill Livingstone, 1978: 16-26.

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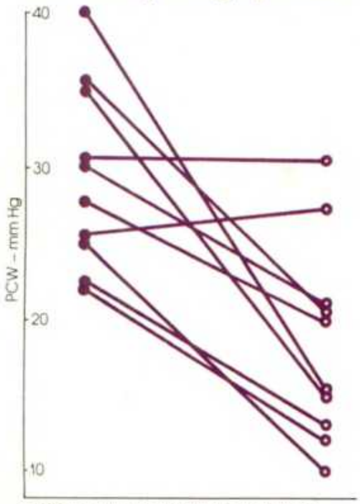
In moderate to severe heart failure unresponsive to digitalis and diuretics the goal of therapy is to reduce elevated pulmonary arterial and left ventricular end-diastolic pressures and increase cardiac output whilst minimizing any fall in arterial pressure.[1]

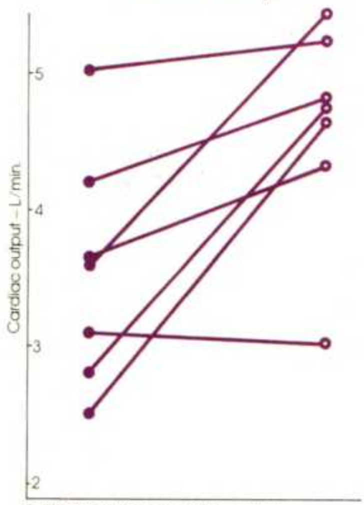
Pulmonary wedge pressure



1. Effects of isosorbide dinitrate (Isoket) on pulmonary capillary wedge pressure.

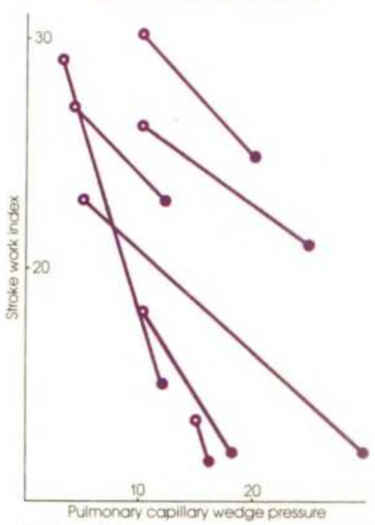
PRIOR TO ISOKET ● ON "OPTIMAL" DOSE OF ISOKET ○

Cardiac output



2. Effects of Isoket on cardiac output.

LV Function curves



3. Effects of Isoket on left ventricular function curves.

isoket* ampoules

(Isosorbide dinitrate 1mg/ml)

proven effective in heart failure

Isoket was administered i.v. in doses of 2-7 mg/hour to 10 patients suffering from extreme pump failure refractory to conventional therapy. Seven patients had severe coronary disease with recurrent infarctions; 5 receiving Isoket during an acute event and in 3 of them severe mitral regurgitation was documented. Three other patients received Isoket just prior to surgery with heart failure consequent to a ruptured ventricular septum, aortic insufficiency and a severely leaking mitral prosthesis.

Marked haemodynamic improvement during Isoket manifested by decrease of pulmonary wedge pressure (PWP) and systemic vascular resistance with increase of cardiac output was obtained in 7 of the 10 patients studied.

Mean arterial pressure was "markedly and favourably affected in those patients who had high initial pressures. The lower arterial pressures remained stable or even increased a little in two patients." Heart rate and the transmyocardial gradient were not deleteriously affected.

Isoket also produced a complete abolition of the mitral regurgitation as evidenced by the disappearance of the giant 'V' wave on the PWP tracings.

The authors concluded that Isoket appears to be "a highly effective and rather safe drug in properly monitored patients with pump failure."[2]

Prescribing Information

Presentation Ampoules containing 10 mg Isosorbide dinitrate in 10 ml of colourless sterile isotonic saline. **Uses** Isoket is indicated in the treatment of unresponsive left ventricular failure secondary to acute myocardial infarction, unresponsive left ventricular failure of various aetiology and severe or unstable angina pectoris. Isosorbide dinitrate is a vasodilator, reducing the afterload and especially the preload of the heart. It influences the oxygen supply to ischaemic myocardium by causing the redistribution of blood flow along collateral channels and from epicardial to endocardial regions. It also reduces oxygen demand by increasing venous capacitance, causing pooling of blood in peripheral veins thereby reducing ventricular volume and heart wall distension. **Dosage and Administration** Dosage The dose employed must be adjusted according to the patient's response. In general, a dose of between 2 and 7 mg per hour is suitable, although doses as high as 10 mg per hour may be necessary. Children The safety and efficacy of Isoket has not yet been established in children. Administration Isoket is a concentrated solution and should never be injected directly. It should always be administered as an intravenous admixture with a suitable vehicle such as Sodium Chloride Injection B.P. or Dextrose Injection B.P. Prepared Isoket admixtures are always given by intravenous infusion or with the aid of an infusion pump. During administration, there should be close monitoring of the patient's blood pressure and pulse. Admixtures are prepared by exchanging the required volume of Isoket with an equal volume of the infusion vehicle. **For example, if a dose of 6 mg per hour is required, 50 ml of Isoket (equivalent to 5 x 10 ml ampoules) should be added to 450 ml of the infusion vehicle to give a final volume of 500 ml. This admixture now contains 1 mg in 10 ml and the required dosage can be obtained by giving 60 ml per hour which is equivalent to a drip rate of 60 paediatric micro-drops per minute or 20 standard drops per minute. This drip rate provides enough solution for an infusion time of 8 hours and 20 minutes. Contra-indications and Warnings, etc.** Contra-indications Isoket should not be used in the treatment of cardiogenic shock unless some means of maintaining an adequate diastolic aortic pressure are undertaken. Isoket is contra-indicated in circulatory collapse and severe hypotension. Precautions Close attention to pulse and blood pressure is necessary during the administration of Isoket infusions. Adverse Effects Whilst sharp falls in systemic arterial pressure can give rise to symptoms of cerebral flow deficiency and decreased coronary perfusion, clinical experience with Isoket has shown that this is not normally a problem. This is consistent with the known vasodilatory effects of isosorbide dinitrate which occur predominantly on the venous rather than the arterial side of the circulation. In common with other nitrates, headache and nausea may occur during administration. **Pharmaceutical Precautions** Compatibility **Isoket contains isosorbide dinitrate in isotonic saline and is compatible with commonly employed infusion solutions. No incompatibilities have so far been demonstrated. Isoket is compatible with glass infusion bottles and infusion packs made of polyethylene, e.g. Polyfusor (Boots) or Bottle-Paks and Flat-Paks distributed by Dylade, Cheshire. Isoket may be infused slowly using a syringe pump with a glass or rigid plastic syringe (Gillette Sabre syringe or Brunswick Disposable Plastipak syringes).** Isoket is incompatible with infusion bags and administration sets made from PVC and a loss of activity of up to 40% is possible on prolonged contact, e.g. 8 hours. Loss after 1 hour is approximately 30%. The use of PVC containers should therefore be avoided, e.g. Viaflex (Travenol) or Steriflex (Boots). **Legal Category** POM. **Package Quantities** Each pack contains ten ampoules of Isoket. **Further Information** Nil. **Product Licence** PL 4438/0001. **Basic NHS Cost** £49.50 per pack of 10 ampoules.

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SCHWARZ

A copy of this clinical paper, further information and a data sheet are available from:
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*Trade Mark

1. W.W. Parmley and K. Chatterjee: "In coronary care: Congestive heart failure." American Heart Association (1977).
2. Rabinowitz B et al. In Nitrates II, 2nd Int. Nitrate Symp., Eds. Rudolph & Schrey, Urban & Schwarzenberg (1980).

etter choice than beta-blockers in hypertension

Baratol works in a more logical way than beta-blockers

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indoramin

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'rescribing Information: For full information see product data sheet. **BARATOL Presentation**: Baratol tablets contain indoramin hydrochloride: the 25mg tablets are blue and the 50mg tablets are green. **Uses**: All grades of essential pertension. **Dosage and administration**: For full details see Data Sheet. Initial dose 25mg bd for all patients. Dose titration. Dosage should be titrated at 2 week intervals to control B.P. to a maximum of 200mg daily. The anti-hypertensive effect is hanced by concomitant administration of a thiazide diuretic or a beta-adrenoceptor blocking drug. **Contra-indications, Warnings, etc** *Contra-indications* – Patients with established heart failure or patients under treatment with MAOI's. ecautions – Drowsiness is sometimes seen in the initial stages of treatment or when dosage is increased too rapidly. Patients should be warned not to drive or operate machinery until it is established that they do not become drowsy while ing BARATOL. Incipient cardiac failure should be controlled with diuretics and digitalis before treatment with BARATOL. Caution should be observed in patients with hepatic or renal insufficiency or Parkinson's disease. Animal experiments icate no teratogenic effects but BARATOL tablets should not be prescribed for pregnant women unless considered essential by the physician. *Side-effects* – Sedation occurs in some patients but is rarely intolerable and is ually overcome by a modest reduction in dosage. Less commonly: dry mouth, nasal congestion, weight gain, dizziness, failure of ejaculation and depression have also been noted. **Treatment of overdosage** – See product ta sheet. **Legal Category**: POM. **Package quantities**: Bottles of 100. **Basic NHS Price**: 25mg 100s £11.00, 50mg 100s £19.50. **Hospital Price**: As per local contract. **Product Licence number**: 25mg tablets PL0011/0071, PA 34/1. 50mg tablets PL0011/0058, PA 22/34/2. **References**: 1. Marks, P. Data on file. 2. Carballo, R. (1977) in *Arterial Hypertension*. Ed. Velasco M., Excerpta Medica, p129. 3. Archibald, J. L. (1980) *Pharmacology of ti-hypertensive drugs*. Ed. Scriabine A., Raven Press, N.Y. 161. 4. Coltart, J. (1981) *Brit. J. Clin. Pharmacol.*, **12**, 49. 5. Zacharias, F. J. (1981) *Brit. J. Clin. Pharmacol.*, **12**, 105. 6. Fitzgerald, M. V. J. (1981) *Brit. J. Clin. Pharmacol.*, 117. 7. Johnson, E. S. (1981) *Brit. J. Clin. Pharmacol.*, **12**, 131. Further information is available on request. **Wyeth Laboratories**, John Wyeth & Brother Ltd., Taplow, Maidenhead, Berks. *Trade marks BAR/J/03/282

Wyeth

Low levels of HDL are associated with an increased risk of CHD.[1] Patients who fail to respond adequately to diet may benefit from Bezalip which raises HDL whilst lowering excessive cholesterol, triglyceride, LDL and VLDL. Many treatments, including diet, have no known effect on or even adversely affect HDL.[2]

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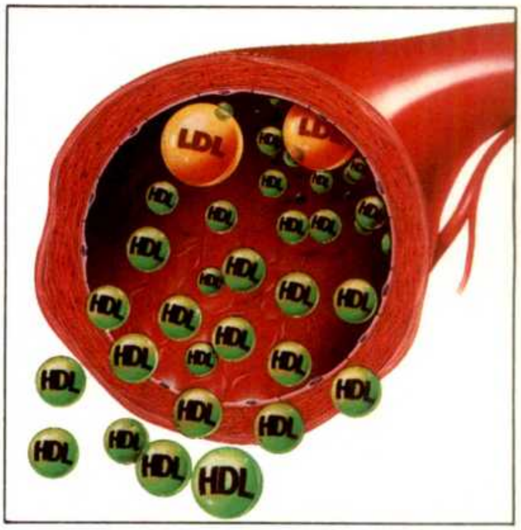
New

Bezalip

bezafibrate



Bezalip has been shown to be more effective than clofibrate in reducing cholesterol, triglyceride, LDL and VLDL and in raising the protective factor HDL[1,2]

Prescribing Information: Presentation Bezalip tablets each containing 200mg bezafibrate. **Indications** Therapy in fully diagnosed hyperlipidaemic states (Fredrickson types IIa, IIb, III, IV & V) which warrant treatment and do not respond adequately to diet alone. **Dosage** 3 tablets (600mg bezafibrate) daily in divided doses. **Contra-indications** Severe hepatic and renal dysfunction, nephrotic syndrome, primary biliary cirrhosis. Not recommended in pregnant or breast-feeding women. **Warnings & Precautions** Dosage of anti-coagulant therapy should be reduced to 50% initially and then titrated to the patient's response. A reduced dosage of Bezalip is required in mild to moderate renal dysfunction. Adverse effects rarely occur; may include feelings of fullness of the stomach, a myositis-like syndrome, disorders of potency and hypersensitivity. No increase in cholelithiasis. **Packs and Basic NHS Cost** Packs of 100 & 500 tablets. 100 tablets, £10.56. **Product Licence Number** PL0075/0036. Further information available on request.

1. *JAMA*, **62** (1977) 707
2. Manufacturers' Literature
3. Lipoproteins and Coronary Heart Disease, Witzstrock Publishing House, New York (1980) 185-188
4. *Ibid.* 192-195
5. *Munch. med. Wschr.* **122, 5** (1980) 165-168
6. Diet and Drugs in Atherosclerosis, eds. G. Noseda, B. Lewis, R. Paoletti, Raven Press, New York (1980) 137-142

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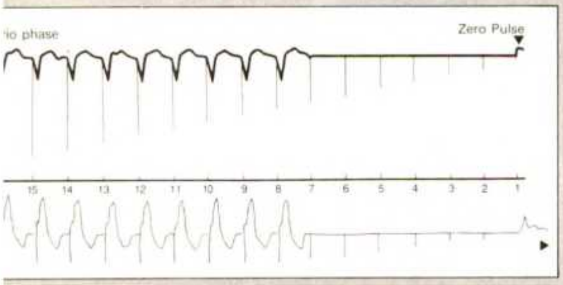
nens-Elema were the pioneers ardiac pacemakers; indeed, in 8 we were the only company in world offering an implantable emaker for general clinical use. ay we are still in the forefront of emaker development. For mple, the multi-programmable del 668 used in combination with



vitreous carbon-tip lead, has ny significant advantages, all ding up to a truly universal pace-ker system for multi-purpose ical use.

systems approach

design philosophy behind the del 668 is the systems approach; chnique which has been applied all the component parts and illary systems. This makes the tem superior, not just in terms of ction, but also in terms of quality, ting, reliability and cost.

satility & reliability

incompatible qualities for a emaker? – Perhaps at first sight, when one realises the amount of elopment that has gone into the 668 pacemaker system then the claim is fully justified.

The 668 pulse generator can be programmed to meet most pacing requirements and is, therefore, probably the most versatile unit currently available.

The adjustable pulse duration and variable pulse amplitude in combination with the low-threshold carbon-tip lead affords the model 668 prolonged service life, with maintained safety margins.

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The 668 generator can be programmed for the six key parameters: pulse rate, pulse duration, pulse amplitude, sensitivity, refractory period and hysteresis. In addition, the 668 has the unique Vario function – a non-invasive technique for determining the true voltage threshold. The Vario cycle, which is initiated by the test magnet, consists of 15 pulses of decreasing amplitude. Knowing the difference in each step, it simply becomes a matter of counting the pulses on the EKG – strip which does not depolarise the heart. The figure multiplied by the known voltage difference between the steps, gives you the true voltage threshold.

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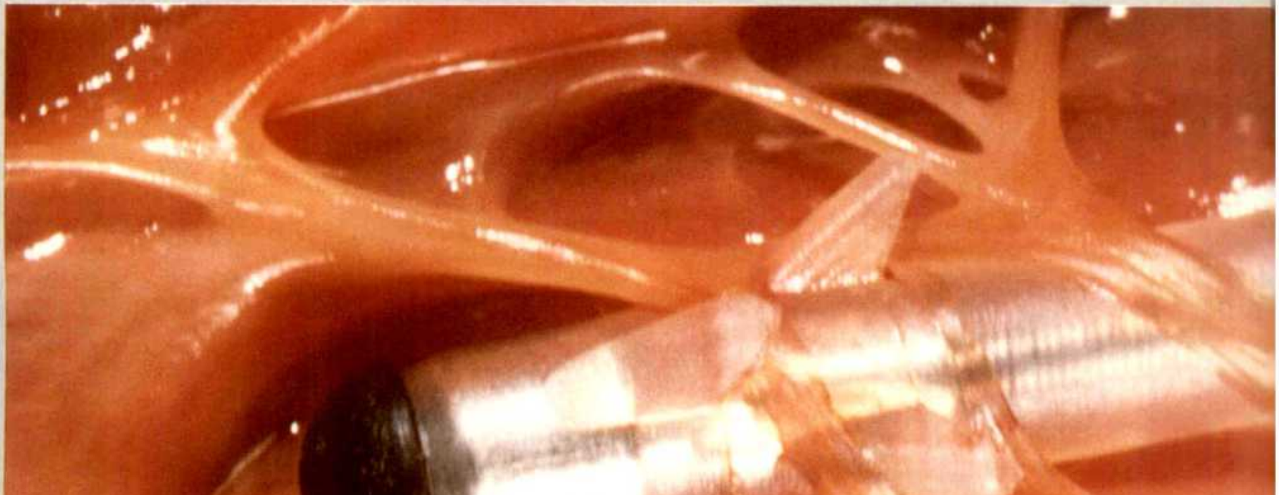

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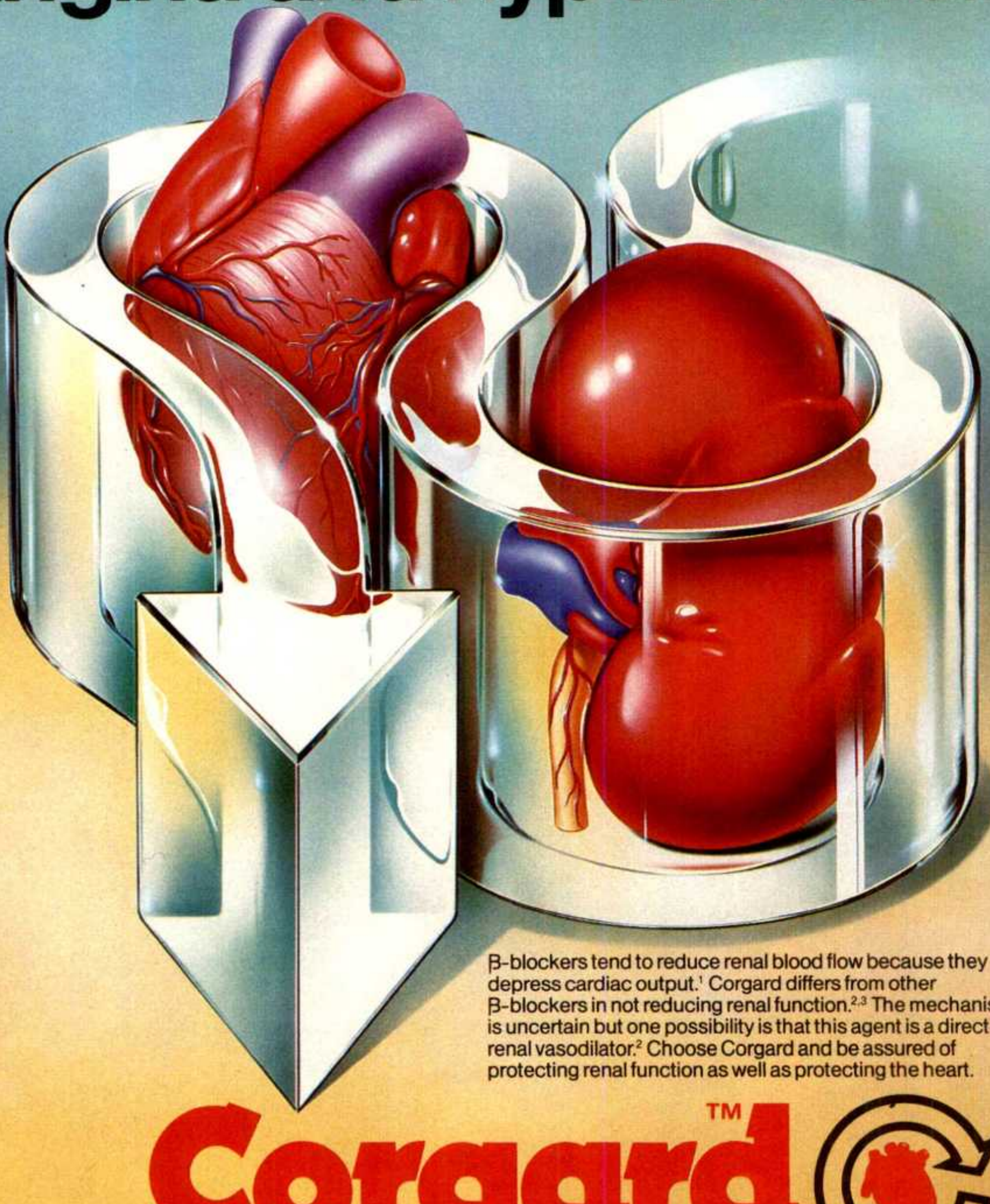

β-blockers tend to reduce renal blood flow because they depress cardiac output.[1] Corgard differs from other β-blockers in not reducing renal function.[2,3] The mechanism is uncertain but one possibility is that this agent is a direct renal vasodilator.[2] Choose Corgard and be assured of protecting renal function as well as protecting the heart.

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DC50281

Corgard
nadolol
tablets

Prescribing Information

Presentation White round biconvex tablets. 80 mg: scored on one side and engraved "Squibb" '241' containing nadolol 80 mg. 40 mg: engraved "Squibb" '207' containing nadolol 40 mg. **Indications** Corgard is indicated in the long-term management of angina pectoris and hypertension. **Dosage and administration** Dosage should be individually titrated. In elderly patients, particularly those with angina pectoris, a low initial dose should be used so that sensitivity to side effects may be assessed. Nadolol may be given in a once daily dosage without regard to meals. Angina Pectoris: Initially 40 mg once daily. This may be increased at weekly intervals until an adequate response is obtained or excessive bradycardia occurs. Most patients respond to 160 mg or less daily. The value and safety of daily doses exceeding 240 mg have not been established. Hypertension: Initially 80 mg once daily. This may be increased by a weekly increment of 80 mg or less until an optimum response is obtained. Most patients respond to 240 mg or less, daily, but doses up to 640 mg have been required for a few patients. In some patients it is necessary to administer a diuretic, peripheral vasodilator and/or other antihypertensive agent in conjunction with nadolol in order tc achieve satisfactory response. Treatment of hypertension associated with phaeochromocytoma may require the addition of an alpha-blocking agent. **Contra-indications** Bronchial asthma, sinus bradycardia and 2nd and 3rd degree heart block; cardiogenic shock; right ventricular failure secondary to pulmonary hypertension; congestive heart failure. **Warnings** The normal precautions associated with the use of beta-adrenergic blockers should be followed. Exacerbation of angina and myocardial infarction have occurred after abrupt discontinuation of therapy with beta-adrenergic blocking agents in patients with angina pectoris or other evidence of coronary artery insufficiency. When discontinuing long-term nadolol therapy the dosage should be reduced gradually over a period of at least two weeks. There have been reports of skin rashes and/or dry eyes associated with the use of beta-adrenergic blocking drugs. The reported incidence is small and in most cases the symptoms have cleared when the treatment was withdrawn. Discontinuance of the drug should be considered if any such reaction is not otherwise explicable. Caution is advised in the presence of impaired renal or hepatic function, obstructive airways disease and diabetes mellitus. Care should be taken in administering nadolol during and within 2 weeks of administration of adrenergic augmenting psychotropic drugs such as monoamine oxidase inhibitors. The safety of nadolol in pregnancy has not yet been established, and nursing mothers should only receive nadolol if deemed essential. **Side-effects** These resemble those reported with other beta-blocking drugs and rarely require withdrawal of treatment. Those reported infrequently include gastro-intestinal effects, bradycardia, fatigue, light-headedness, cold extremities, insomnia, paraesthesia and dryness of the mouth. Cardiac insuffiency, hypotension and AV block have occurred on rare occasions. Overdosage or exaggerated response should be treated supportively and symptomatically. **Legal category** Prescription only. **Product Licence Numbers** 80 mg – 0034/0186 40 mg – 0034/0185. **Package Quantities** Bottles of 100 tablets. Cost per 80 mg tablet, 16p. Cost per 40 mg tablet, 11p. ▼ Special reporting to CSM required. Corgard is a Trade Mark of E.R. Squibb & Sons Ltd.

References
1. Lancet 1980; 1: 693 2. Br J clin Pharm 1979; 7: (Suppl 2) 219S
3. In: Gross F, ed. International Experience with Nadolol – a long-acting β-blocking agent: symposium, Paris, December 5–7, 1980 London: R Soc Med No 37 1981 25–30

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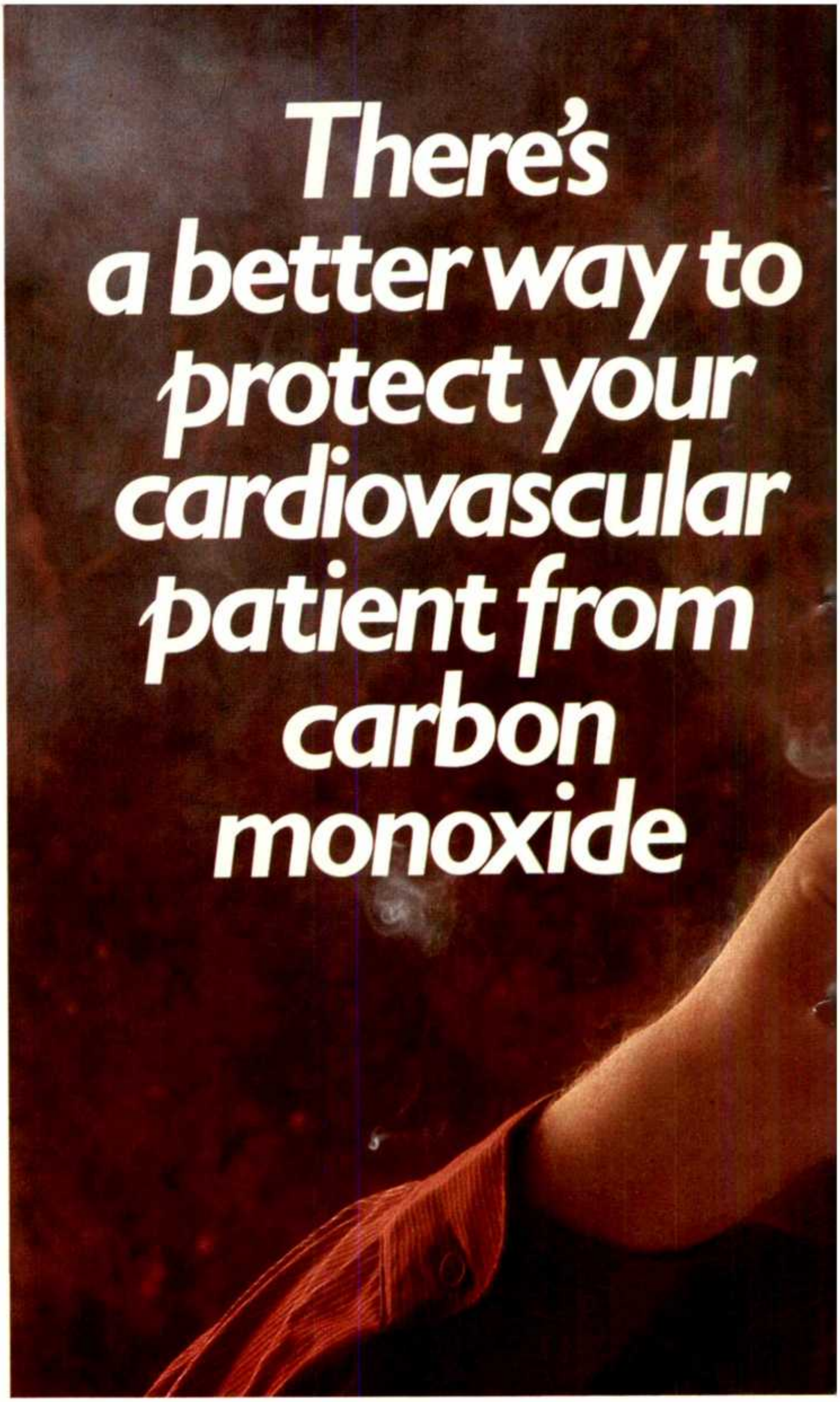
There's a better way to protect your cardiovascular patient from carbon monoxide

Nicorette 2 mg or 4 mg nicotine resin in a chewing gum base. **Indication** An aid to smoking cessation. **Dosage and Administration** Start treatment with 2 mg gum in all patients. Some smokers may need to be changed to the 4 mg gum after a trial period of approximately 2 weeks. Each piece should be chewed slowly for 30 minutes. Nicorette consumption should be reduced after 2-6 months, before finally being withdrawn. Average daily dose: 10 x 2 mg pieces. Maximum recommended daily dose: 15 x 4 mg pieces. **Precautions** Peptic ulcer, gastritis, angina, coronary disease. **Contra-indications** Pregnancy and childhood. **Adverse Reactions** Occasional: hiccups, indigestion, hypersalivation, throat irritation. **Further Information** Overdosage can occur only if many pieces are chewed simultaneously. Even then, the risk of poisoning is extremely remote as nausea or vomiting would occur at an early stage. The risk of poisoning by swallowing the gum is also remote because of the very slow release of nicotine from unchewed gum. **Package Quantities** Box of 105 pieces, in blister strips of 15 pieces, 2 mg £4.20, 4 mg £6.72. (Trade prices, correct at time of printing.) PL Nos 0458/0020, 0458/0021 PA Nos 115/7/1, 115/7/2.

References: 1. Aronow WS. Effect of Cigarette Smoking and of Carbon Monoxide on Coronary Heart Disease. Chest 1976; 70: 54-157. 2. Tibblin G, Wilhelmsen L, Werkö L. Risk Factors for Myocardial Infarction and Death Due to Ischemic Heart Disease and Other Causes. American Journal of Cardiology 1975; 35: 514-522. 3. Russell MAH, Wilson C, Taylor C, Baker CD. Brit med J 1979; 2: 231-235. 4. Raw M, Jarvis MJ, Feyerabend C, Russell MAH. Brit med J 1980; 281: 481-482.

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Smoking means carbon monoxide. Carbon monoxide means less oxygen for the tissues and possibly an increased deposition of atheromatous plaques on the artery wall.[1]

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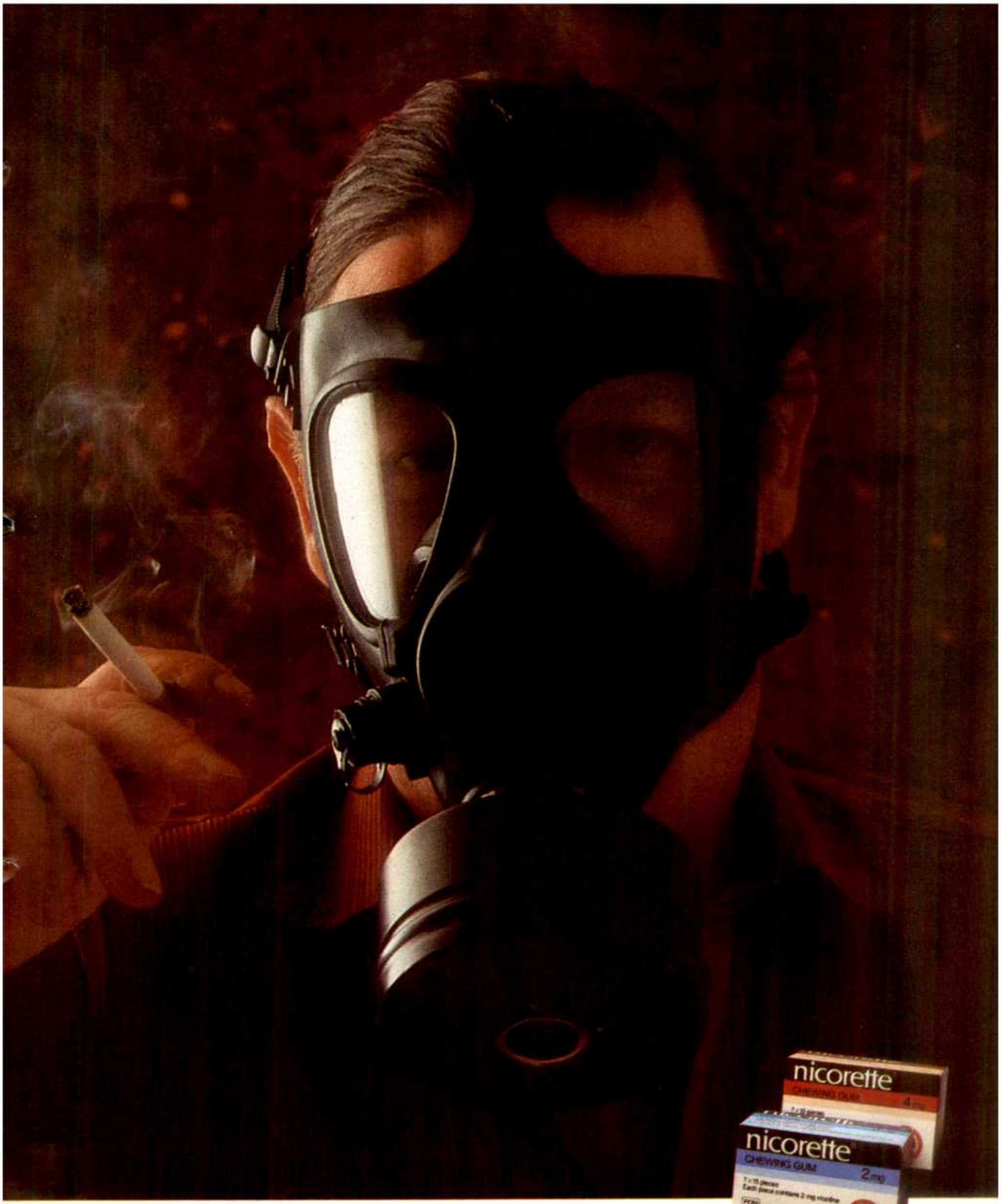

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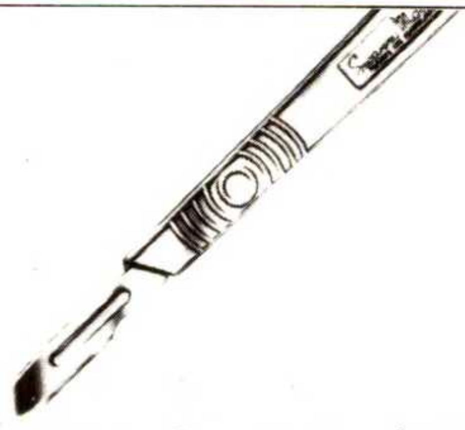

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Electrocardiograms and 13 year cardiovascular mortality in Busselton study

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SUMMARY In 2119 unselected Busselton subjects 40 to 79 years of age, the 13 year mortality from cardiovascular disease was significantly higher in those whose initial electrocardiogram showed Q and QS patterns, left axis deviation, ST depression, T wave depression, flat or biphasic T waves, atrial fibrillation or flutter, and ventricular extrasystoles.

In angina-free subjects whose electrocardiographic codes occurred in isolation from any other electrocardiographic abnormality, ventricular extrasystoles were associated with significantly higher mortality from cardiovascular disease compared with controls.

Since 1966, the Busselton population has been the subject of a longitudinal study of cardiovascular mortality.[1] Resting electrocardiograms were associated with significantly increased six year mortality in those with suspected ischaemic heart disease, and in those with probable ischaemic heart disease to factors of seven to nine times and 20 times, respectively.[2] The present paper outlines the 13 year cardiovascular mortality in 2119 unselected subjects 40 to 79 years of age, related to their electrocardiograms recorded in 1966.

Methods

Resting electrocardiograms were recorded on Nihon Kohden machines, model MC-11 and Model MC-3, with a paper speed of 25 mm per second. These machines fulfilled the performance recommendations of the AHA Committee on Electrocardiography 1967[3] except in the high frequency range, where constant amplitude sinusoidal input signals of 100 Hz were reduced to 50%. The maximum reduction should be no more than 30%. Such a defect could in part affect the prevalence of tall R waves. There were no specific intervals between the time of the meal and recording of the electrocardiograms, but approximately 10% of subjects had their electrocardiograms recorded about one and a quarter hours after a 50 g glucose drink. For the remaining subjects, there was a longer interval.

All electrocardiograms have been classified according to the Minnesota Code[4] by five trained observers working independently under the guidance of a consultant cardiologist (GNC). All subjects answered the chest pain questionnaire of Rose.[5]

One thousand and fifty-six men and 1063 women were studied. Mortality in this group between January 1967 to December 1979 was confirmed by the Registrar of Deaths in Perth, Western Australia. Survivor status was established by local contact and by checking all compulsory electoral rolls in Western Australia. Twenty-one men and 18 women could not be traced. All missing subjects were checked against the Registrar's files for possible deaths. The ICD 8th revision (1968) codes used to determine mortality resulting from cardiovascular disease were 390-458 and 746-747. The 13 year cardiovascular disease mortality in control subjects with a normal electrocardiogram was compared in each instance with the cardiovascular disease mortality of those found with the specified abnormality.

Using the total 40 to 79 year population as a basis, standardised mortality rates for specific electrocardiographic codes and for the "normal electrocardiogram" population were calculated by the direct method.[6] The standardised mortality rate for the "normal electrocardiogram" population was compared with that for the population with a specific electrocardiographic code, expressed first as a difference and second as a ratio. The difference was used to calculate an approximate standardised normal deviate, and the appropriate test of significance performed.

Initially, all populations were divided into eight five-year age groups, for each sex. It was decided to standardise using only those age-groups where the

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Table *Thirteen year cardiovascular mortality in 2119 subjects for specific electrocardiographic codes compared with population wi*

Specific code		*No. of age contrib. groups*	*No.*	*No. of deaths*	*Mortality ratio*†	*Z*
1.1–1.3	Q and QS patterns	3	19	12	3·7	4·86***
2.1	Left axis deviation > −30°	7	68	20	1·6	2·11*
4.1	ST and segment depression 1 mm or more	0	—	—	—	—
4.2	ST 0·5 to 1 mm horizontal or downward	1	5	4	2·1	1·74
4.3	ST downward by 0·5 mm	0	—	—	—	—
5.2	T wave negative 1 to 5 mm	4	32	21	3·5	5·89***
5.3	T wave flat or biphasic <1 mm	2	17	11	2·3	2·88**
8.1(3)	Ventricular extrasystoles >10%	1	5	2	2·7	1·47
8.3(0)	Atrial fibrillation or flutter	0	—	—	—	—
8.9(3)	Ventricular extrasystoles infrequent	5	33	11	2·0	2·37*
8.1(3)† 8.9(3)	All ventricular extrasystoles	7	58	20	2·1	3·53***

*p<0·05 **p<0·01 ***p<0·001.

†Mortality ratios represent mortality from cardiovascular disease seen with the specific electrocardiogram divided by that of the population with nor electrocardiogram in age standardised rates.

specific electrocardiographic code population had at least five people at risk. In this data set all eight age groups were used in calculating rates and ratios on only four occasions, and then only when the sexes were combined.

Finally, two different methods of determining the specific electrocardiographic code populations were used—firstly, where the particular code existed without regard to any other code that may have been present: these results are presented in the Table for the 2119 unselected subjects aged 40 to 79 years. The second method analysed the mortality in 1497 subjects free of angina for each electrocardiographic code in isolation from any other code.

Results

The Table outlines the findings in the 2119 unselected subjects aged 40 to 79 years. Mortality from cardiovascular disease was significantly higher in those whose initial electrocardiogram showed Q-QS patterns, left axis deviation, ST junction and ST segment depression, negative T waves, flat or biphasic T waves, atrial fibrillation or flutter, ventricular extrasystoles more than 10% of all complexes, and infrequent ventricular extrasystoles.

In 1497 subjects free of angina, the analysis of those electrocardiographic codes without any other coexisting electrocardiographic codes (not tabled with the results of the unselected subjects in the Table) has shown that infrequent ventricular extrasystoles were the only electrocardiographic code in isolation to be associated with a raised risk of cardiovascular disease. The mortality ratio was 2·1 for both sexes in six contributing age groups, with 11 deaths in 46 subjects with a Z value of 2·55 ($p<0·05$). The cardiovascular disease mortality ratio for all types of ventricular extrasystoles was 2·4 for both sexes, with a Z value of 3·44 ($p<0·001$) in seven contributing age groups, showing 15 deaths in 61 subjects.

Discussion

VENTRICULAR EXTRASYSTOLES

A recent review[7] concluded that ventricular extrasystoles occurring in subjects without clinical evidence of cardiac disease appear not to be associated with an increased incidence of either sudden death or death. In contrast to these conclusions, Blackburn *et al.*[8] reported an increased incidence of coronary heart disease in those with ventricular extrasystoles compared with carefully matched controls. The ratio of expected to observed was 1·9, the number being too small to reach levels of significance. These findings resembled those in Busselton where ventricular extrasystoles in angina-free individuals without coexisting electrocardiographic abnormalities were associated with a significant increase in mortality from cardiovascular disease.

Q AND QS, T WAVE CHANGES, AND ATRIAL FIBRILLATION

In Busselton unselected subjects, Q and QS changes, ST segment and T wave changes, atrial fibrillation, and left axis deviation were associated with significantly greater mortality from cardiovascular disease. The numbers showing these abnormalities in selected subjects were too small to be of significance.

In 18 403 unselected civil servants 40 to 64 years, Rose *et al.*[9] reported significantly increased coronary heart disease mortality in those with small Q waves, left axis deviation, flat or inverted T waves, and left *mal electrocardiograms each standardised in five year age groups for Busselton population 40 to 79 years*

nen					*All subjects*				
of age rib. ps	*No.*	*No. of deaths*	*Mortality ratio*	*Z*	*No. of age contrib. groups*	*No. of all subjects*	*No. of deaths*	*Mortality ratio*	*Z*
	12	7	2·1	1·9	7	58	29	3·82	7·60***
	41	12	2·1	2·42*	8	119	32	1·64	2·461*
	—	—	—	—	3	20	15	3.82	5.53***
	6	3	2·2	1·43	5	37	18	2·81	4·69***
	19	11	3·0	3·06**	6	51	26	2·81	5·14***
	39	29	5·2	8·43***	6	79	53	4·5	11·07***
	33	14	3·0	4·03***	7	69	31	3·3	6·64***
	—	—	—	—	2	10	4	2·8	2·29***
	—	—	—	—	1	5	4	2·4	2·04*
	32	12	2·7	3·40***	8	84	25	2·2	3·93***
	34	14	3·0	4·02***	8	106	35	2·6	5·62***

bundle-branch block. In symptomless normotensive subjects, only those with prominent Q waves and atrial fibrillation showed excess mortality from coronary heart disease.

In an international study[8] of 12 770 men of 40 to 59 years, there was a significantly increased five year incidence of coronary heart disease in those with major Q and QS complexes, with negative T waves, and in those with atrial fibrillation compared with carefully matched control subjects. An increased risk of stroke from emboli was reported[10] in Framingham subjects with atrial fibrillation.

LEFT VENTRICULAR HYPERTROPHY

An increased cardiovascular disease mortality has been described[11] in those with left ventricular hypertrophy, compared with the population at large. In Busselton, left ventricular hypertrophy was not associated with significantly increased cardiovascular mortality.

LEFT BUNDLE-BRANCH BLOCK AND RIGHT BUNDLE-BRANCH BLOCK

Schneider *et al.*[12] have recently reported that 50% of 55 Framingham subjects with left bundle-branch block had died within 10 years of its onset with only 11% remaining clinically free of cardiovascular abnormalities. The mean age of onset for left bundle-branch block was 62 years. Schneider *et al.*[13] also reported on newly acquired right bundle-branch block in 70 Framingham subjects over a period of 18 years, mortality from cardiovascular disease being almost three times greater in these subjects than in an age matched sample of the population at large. Busselton subjects showed no significant increase in cardiovascular disease mortality for left and right bundle-branch block in the analysis of age specific mortality.

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Ambulatory electrocardiographic recording in endurance athletes

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SUMMARY Data from ambulatory electrocardiographic recording in 35 highly trained endurance athletes and in 35 non-athletic controls of similar ages are given. The minimal, mean hourly, and maximal heart rates were significantly lower in the athletes. Thirteen athletes (37·1%) but only two controls (5·7%) had sinus pauses exceeding 2·0 seconds. First degree atrioventricular block was observed in 13 athletes (37·1%) and five controls (14·3%), second degree Wenckebach type block in eight athletes (22·9%) and two controls (5·7%), and second degree block with Mobitz II-like pattern in three athletes (8·6%) and no control. All athletes with Mobitz II-type pattern also had first degree and Wenckebach-type second degree atrioventricular block. The behaviour of sinus rate on development of atrioventricular block varied, not only interindividually but also intraindividually, from absence of change to an increase or decrease in most subjects in both study groups. A decrease in sinus rate on appearance of atrioventricular block was found constantly in only two athletes and one control. Atrioventricular dissociation with junctional rhythm occurred in seven athletes (20%) and with ventricular rhythm in one athlete. Neither of these phenomena was seen in the group of controls. The athletes had slightly fewer ventricular extrasystoles than controls, and no athlete had ventricular tachycardia, whereas two controls had ventricular tachycardia.

The spectrum of changes in conventional resting electrocardiograms in athletes is wide, and relatively well documented.[1-14] Knowledge concerning variations in rhythm and conduction and the incidence of ventricular extrasystoles in athletes, however, is still deficient. Because variations usually occur transiently, the chance of detecting them via conventional resting or exercise electrocardiograms is slight. Studies using ambulatory electrocardiographic recording have shown that a wide range of transient variations and disturbances in cardiac rhythm and atrioventricular conduction can be detected even in ordinary healthy subjects.[15-18] As far as the authors know the only studies so far published concerning changes detected by ambulatory electrocardiographic recording in athletes are a few abstracts containing only limited amounts of information.[19-21] The present study was undertaken to discover what range of changes in cardiac rhythm and atrioventricular conduction, and what incidence of ventricular extrasystoles might be detected by ambulatory electrocardiographic recording in endurance athletes as compared with controls.

Subjects and methods

SUBJECTS

Volunteers for this study consisted of 35 male endurance athletes, aged 23·1±6·1 (mean ± SD) years, and 35 controls, aged 23·0±5·8 years. The athletes were top-class national long-distance runners, skiers, and basketball players. To obtain the athletes for the study, a club for runners and skiers and a particular sports group of army conscripts were approached. Athletes fulfilling the following criteria were accepted for the study: at least five years of intensive physical training, absence of history of cardiovascular disease, and of any other disease known to affect the cardiovascular system; normal findings on a clinical examination, no changes in 12 lead resting electrocardiogram, and chest *x*-ray film not attributable to an athletic heart[1 8-14 22-24]; not permanently under medication, and not under medication at the time of the study; non-smoker; absence of upper respiratory infection during a one month period before the study.

This study was supported by a personal grant (RK) from the Paavo Nurmi Foundation.

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The controls were medical students and army conscripts. The criteria for acceptance were the same as those listed above, with the following exceptions: no regular intensive physical training; normal 12 lead electrocardiogram and chest *x*-ray.

AMBULATORY ELECTROCARDIOGRAM

The recordings were performed using a two-channel electrocardiographic tape recorder (Model 445, Avionics). The exploring electrodes were placed on the lower end of the sternum and on the fifth rib at the left anterior axillary line. Recordings were started at 4.00 pm and concluded at 8.00 am. The subjects were directed to go to bed around 10.00 pm and rise around 6.00 am. Activities during recording were not restricted, except that physical training was not allowed. Consumption of alcoholic beverages was forbidden.

Tapes were analysed using a commercial analyser (Electrocardioscanner Model 660, Avionics). All tapes were assessed by the authors. Initial scanning was performed at 60 times normal speed. In cases of definite or suspected findings, the scanner was switched to normal speed, and the findings printed on an electrocardiographic chart (speed 25 mm/s) for detailed analysis. All findings reported here were taken from such electrocardiographic charts. Each tape was screened between three and 10 times at 60 times normal speed. Mean hourly heart rates (number of heart beats per hour divided by 60) were counted by the scanner.

DEFINITIONS

Definitions and criteria used in the present study are given at the beginning of each results section concerned.

STATISTICAL METHODS

Student's unpaired t test and the χ^2 test were used in statistical analysis of the results.

Results

HEART RATE

Mean hourly heart rates for both groups studied are shown in Fig. 1. The lowest nocturnal heart rate, calculated using the six slowest consecutive sinus beats, was 37·7±4·3 (mean ± SD) beats/min (range 24 to 48) for athletes and 45·4±6·3 beats/min (range 33 to 63) for controls ($p<0{\cdot}001$). The maximal heart rate when awake, calculated analogously, was 124·5±17·3 beats/min (range 100 to 164) for athletes and 137·3±18·5 beats/min (range 87 to 168) for controls ($p<0{\cdot}01$).

SINUS PAUSES

Thirteen athletes (37·1%) and two controls (5·7%) had PP intervals exceeding 2·00 s in sinus rhythm without second degree atrioventricular block ($p<0{\cdot}01$). The longest PP interval among athletes was 2·76 s and among controls 2·60 s. All sinus pauses exceeding 2·00 s occurred between 10 pm and 6 am.

ATRIOVENTRICULAR CONDUCTION

First degree atrioventricular block (PR interval>0·22 s) was detected in 13 athletes (37·1%) and five controls (14·3%) ($p<0{\cdot}05$) (Table 1 and Fig. 2). In five athletes and two controls the PR interval was prolonged con-

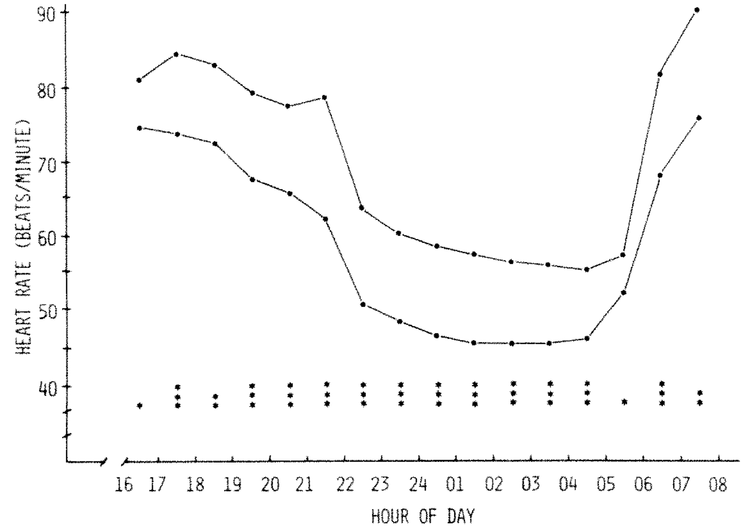

Fig. 1 *Mean hourly heart rates in athletes (lower line) and controls (upper line).* $^{*}p<0{\cdot}05$, $^{**}p<0{\cdot}01$, $^{***}p<0{\cdot}001$.

Table 1 *Occurence of atrioventricular block in athletes and controls*

Subject No.	*First degree AV block*	*Second degree Wenckebach AV block*	*Second degree AV block with Mobitz II pattern*
Athletes			
1	+(0·28)*		
2	+(0·32)	+	+
4	+(0·32)		
8	+(0·24)		
12	+(0·42)	+	+
13	+(0·40)	+	
15	+(0·28)	+	
16	+(0·26)	+	+
18	+(0·36)	+	
21	+(0·36)	+	
22	+(0·32)	+	
23	+(0·28)		
35	+(0·54)		
	13/35	8/35	3/35
	37·1%	22·9%	8·6%
Controls			
2	+(0·24)		
13	+(0·40)		
17	+(0·32)	+	
20	+(0·36)	+	
23	+(0·26)		
	5/35	2/35	–
	14·3%	5·7%	

*Numbers in parentheses indicate the longest PR interval.

stantly for at least an hour. In all the other subjects prolongations lasted for only a few seconds or minutes.

Among athletes, there was first degree atrioventricular block during sleep in six cases, during sleep and while awake in four cases, and while awake in three cases. Among controls, atrioventricular block occurred only during sleep. More than one short period of first degree atrioventricular block was found in 11 of the 13 athletes concerned and in all controls. Heart rate at the time of block, calculated from the PP interval preceding appearance of block, varied from 29 to 103 beats/min in athletes and from 33 to 83 beats/min in controls. In all subjects, the PR interval returned to less than 0·20 s with increase in heart rate.

Second degree Wenckebach-type atrioventricular block, defined as gradual prolongation of the PR interval terminating in a nonconducted P wave and a dropped ventricular beat (Fig. 3), was found in eight athletes (22·9%) and two controls (5·7%) ($p<0·05$) (Table 1). The three cases (athletes 12 and 16 and control 20) in whom there was, in addition to typical Wenckebach-type block, disorganised prolongation of successive PR intervals terminating in a blocked beat, a phenomenon sometimes called type III second degree atrioventricular block,[25] were classified here as having second degree Wenckebach-type atrioventricular block. In athletes, block was detected both when awake and when asleep in two cases, while asleep in five cases, and while awake in one case. Among controls, block occurred in all cases during sleep only. In five athletes and one control, block was observed more than once. The level of heart rate when PR prolongation began varied from 33 to 88 beats/min in the athletes and from 45 to 75 beats/min in the controls.

Second degree atrioventricular block with Mobitz II pattern, defined as a nonconducted P wave and a dropped ventricular beat preceded by a constant and

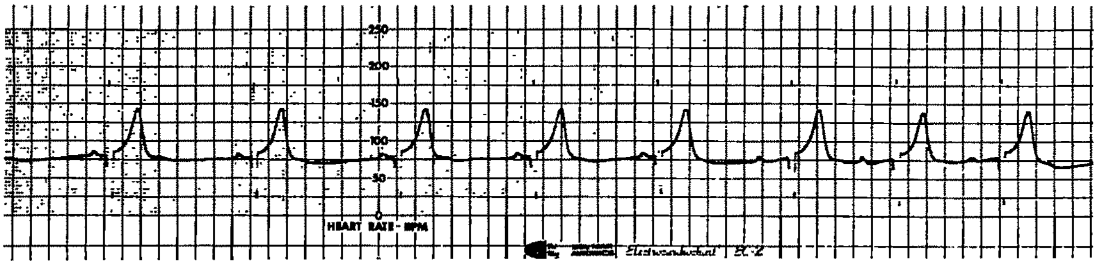

Fig. 2 *First degree atrioventricular block (athlete no. 13) with sinus node acceleration on appearance of atrioventricular block.*

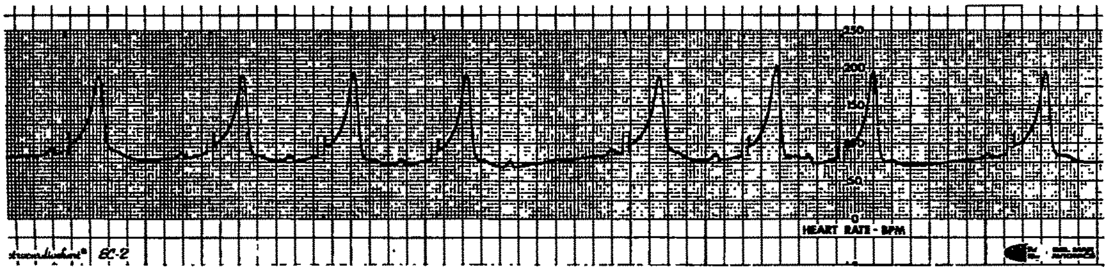

Fig. 3 *Second degree Wenckebach-type atrioventricular block (athlete no. 12).*

followed by the same or a slightly shorter PR interval (Fig. 4), was found in three athletes (8·6%) but no controls (Table 1). In one athlete, block was found several times when awake and when asleep, in another several times only while awake, and in a third twice during sleep. The level of heart rate at the time of the occurrence of block varied from 48 to 93 beats per minute.

As shown in Table 2, the changes in sinus rate at the time of the appearance of atrioventricular block, calculated from the last PP interval before block and the first PP interval during block, varied from none to an increase (Fig. 2) or decrease. Only three athletes constantly had the same kind of sinus rate behaviour on development of block. Two (athletes 15 and 21) had a decrease in sinus rate and one (16) no change. Among the controls, sinus rate behaviour was always the same in two cases. One (control 23) had a decrease and one (control 2) an increase in sinus rate.

Table 2 *Subjects with atrioventricular block grouped according to changes in sinus rate at time of appearance of block*

	First degree AV block		*Second degree Wenckebach AV block*		*Second degree AV block with Mobitz II pattern*	
	*A**	*N†*	*A**	*N†*	*A**	*N†*
O	3		1	1	2	
↑	1	1	2			
↓	2	1	3		1	
O↑	3					
O↓	1					
↓↑		1	1	1		
O↑↓	3	2	1			
Total	13	5	8	2	3	

O, No change in sinus rate, ↑, increase in sinus rate; ↓, decrease in sinus rate; O↑, no change in a given subject on one occasion, increase on another.
*Athletes.
†Controls.

Atrioventricular dissociation with junctional or ventricular rhythm, also called interference dissociation,[25] is defined as dissociation of sinus rhythm from a slightly faster junctional or ventricular rhythm, and results either from slowing of sinus node or a slight acceleration of the lower rhythm (Fig. 5): this was

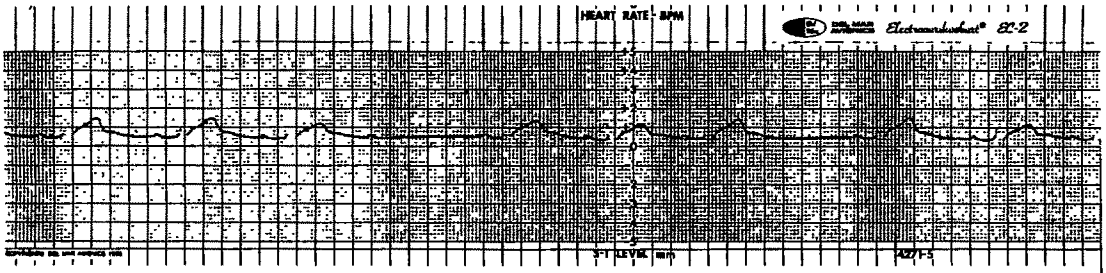

Fig. 4 *Second degree atrioventricular block with Mobitz II-like pattern (athlete no. 16). Note slightly shorter PR interval in the first conducted beat after block.*

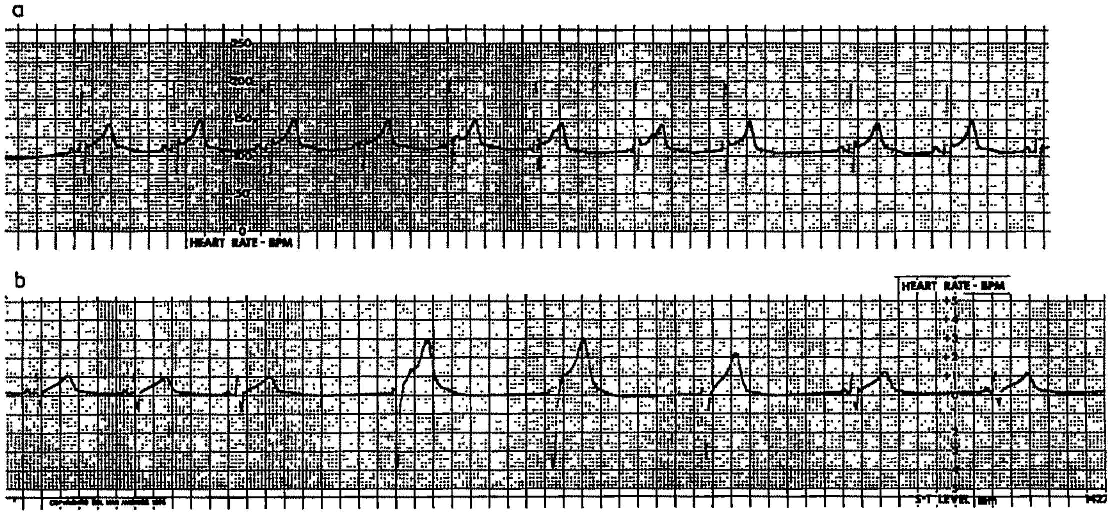

Fig. 5 *Atrioventricular dissociation with (a) junctional rhythm and (b) ventricular rhythm (athletes nos. 5 and 7). Note the positive P wave after QRS complexes in the centre of the electrocardiographic traces.*

found in seven athletes (20·0%) but not in the controls. All athletes had junctional rhythm, and one also had periods of ventricular rhythm. All showed the phenomenon several times. In three of the cases with junctional rhythm and in the case with ventricular rhythm, dissociation was observed both when awake and asleep. Three athletes showed dissociation only during sleep and one only while awake. Of these seven athletes, two had transient first degree atrioventricular block and one had both first and second degree Wenckebach-type atrioventricular block. In all seven athletes, atrioventricular dissociation was attributed to slowing of sinus rate. In one case with junctional rhythm and in the case with ventricular rhythm, dissociation was also occasionally caused by slight acceleration of the lower rhythm. The sinus node rate at which dissociation occurred varied from 26 to 56 beats/minute, when dissociation resulted from slowing of sinus node rate. The rate of junctional rhythm varied from 27 to 68 beats a minute and of ventricular rhythm from 32 to 44 beats a minute. In cases where dissociation resulted from slight acceleration of lower rhythm, it occurred at sinus node rates of between 40 and 51 beats a minute.

VENTRICULAR ARRHYTHMIAS

Table 3 shows ventricular extrasystoles classified according to Jelinek *et al.*[26] The ventricular tachycardias observed in two controls consisted of three and seven beats. One (no. 12) had no additional ventricular extrasystoles. The other (no. 14) had one single ventricular extrasystole in addition to tachycardia. Two controls (nos. 18 and 25) but no athlete had frequent ventricular extrasystoles (on average five an hour). Of the two controls, the first had only unifocal single ventricular extrasystoles and the second had unifocal extrasystoles, both single and in the form of bigeminy. The few ventricular extrasystoles observed in athletes occurred at random throughout the period of recording.

Table 3 *Ventricular extrasystoles in athletes and controls classified according to Jelinek et al.*[26]

*Grade**	*Athletes*	*Controls*
0	23	20
1	10	11
2	0	1
3	2	0
4a	0	1
4b	0	2
5	0	0

*Grade 0, no arrhythmia; grade 1, isolated unifocal ventricular extrasystoles less than 30/h or 1/min; grade 2, isolated unifocal extrasystoles more than 30/h or 1/min; grade 3, multiform ventricular extrasystoles; grade 4a, couplets; grade 4b, ventricular tachycardia; grade 5, early cycle ventricular extrasystoles.

Discussion

RATE AND SITE OF IMPULSE FORMATION

Resting bradycardia in athletes has been attributed both to a relative increase in parasympathetic dominance on pacemaker frequency[27 28] and also to independent slowing of the intrinsic rate of the pacemaker.[29] Despite the significantly lower mean hourly heart rate throughout the period of recording in this study, the pattern of circadian variation in athletes was similar to that in controls. Attainment of minimal heart rates relatively early during the night may reflect overall lower sympathetic tone in athletes.

Sinus pauses exceeding two seconds without second degree atrioventricular block are relatively rare in healthy individuals. They have been seen during ambulatory electrocardiographic recording in two of 50 healthy medical students[16] and in two of 259 healthy subjects aged 40 to 79 years.[30] In the present study they were seen in two of 35 nonathlete controls. In endurance athletes, the incidence of sinus pauses greater than two seconds is significantly greater than in controls. In a group of 20 athletes, the mean of the longest sinus pauses during ambulatory electrocardiographic recording has been found to be two seconds (range 1·60 to 2·80 s).[21] In the present study, 13 of 35 athletes (37·1%) had sinus pauses greater than two seconds. Though the exact mechanisms predisposing to long sinus pauses in athletes remain unclear, they are probably related to factors responsible for sinus bradycardia.

Sinus bradycardia is obviously also the factor making it possible for atrioventricular dissociation with junctional or ventricular rhythm to occur in athletes. Though atrioventricular dissociation with junctional rhythm was not seen in any control in the present study, it cannot, however, be regarded solely as a peculiarity of the athletic heart, because in a population of 122 043 healthy air force personnel, its incidence has been reported to be 0·7/1000.[31] Though the intrinsic pacemaker rate of the atrioventricular node in healthy subjects is usually between 40 and 60 beats a minute,[25 32] the results of the present study show that even in healthy individuals it can fall to as slow as 27 beats a minute.

ATRIOVENTRICULAR CONDUCTION

First degree atrioventricular block has been reported in resting electrocardiograms in athletes[1 4 5 8] and second degree Wenckebach-type atrioventricular block occasionally.[1 7 11] Ambulatory electrocardiographic recording has shown that these types of atrioventricular blocks are by no means exceptionally rare, even in healthy controls. First degree atrioventricular block has been reported to occur in four of 50 (8·0%) medical students,[16] in 11 of 131 (8·4%) boys aged 10 to 13 years,[17] and in nine of 92 (9·8%) boys aged 7 to 11.[18] In the present study it occurred in five of 35 (14·8%) controls. Second degree Wenckebach-type atrioventricular block has been reported to occur in two of 86 (2·3%) instances in a population aged 16 to 65 years,[15] in three of 50 (6·0%) medical students,[16] in 14 of 131 (10·7%) young boys,[17] and in three of 92 (3·3%) boys aged 7 to 11.[18] It occurred in two of 35 (5·7%) controls in the present study. Second degree atrioventricular block of the Mobitz type II was reported to have occurred in one subject in the healthy population studied by Clarke *et al.*[15] but was not reported in any of the other studies mentioned above. It did not occur in the controls in the present study. Using ambulatory electrocardiographic recording, first degree atrioventricular block has previously been found in two of 25 (8·0%)[20] and second degree Wenckebach-type block in three of 25 (12·0%)[20] and eight of 20 (40·0%)[21] athletes. In the athletes in this study the respective incidences were 13 of 35 (37·1%) and eight of 35 (22·9%). In addition, three athletes (8·6%) had second degree atrioventricular block with Mobitz II-like pattern.

There is no unanimity in the medical publications as to whether the definition of second degree Mobitz type II atrioventricular block should include infranodal siting of the block.[33-35] If the site of block is taken into account, there are several occasions on which differentiation between Wenckebach and Mobitz type II blocks in the electrocardiogram is difficult or even impossible, within the limitations introduced by a chart speed of 25 mm/s.[35] The three athletes with Mobitz II pattern in the present study are similar to the subject referred to above in the healthy population studied by Clarke *et al.*,[15] in that all had an abundance of other types of atrioventricular block, third degree block excepted.

The occurrence of atrioventricular block in athletes has been regarded as an expression of relative vagal dominance, and of fluctuation in vagal activity.[25] In animal experiments, vagal stimulation has, indeed, been shown to be capable of producing first and second degree atrioventricular block, Mobitz II pattern included, the site of the block being intranodal.[36] If vagal tone, however, were the sole factor causing atrioventricular block in athletes, a simultaneously demonstrable decrease in sinus rate would also be expected,[33] because the sinus pacemaker may be more sensitive than atrioventricular nodal conduction to vagal influences.[36] Decreases in sinus rate were observed in a number of cases in the present study, but in a substantial number of cases there was no change in sinus rate or an increase at the time of the appearance of atrioventricular block, even in the same subject at different times. Thus, though relative vagal dominance is probably a factor causing atrioventricular block in athletes and, rarely, in controls, the observed variations in sinus rate on appearance of atrioventricular block suggest that there are additional associated mechanisms involved. Vagally-induced atrioventricular block via a hyporeactive sinoatrial node, a phenomenon that has been reported to occur very occasionally in healthy youngsters,[37] cannot be ruled out in the athlete no. 16 in whom sinus rate did not change on any occasion when atrioventricular block appeared, since no tests which would specifically detect a hyporeactive sinoatrial node[37] were conducted.

VENTRICULAR EXTRASYSTOLES

Ventricular extrasystoles up to short bursts of ventricular tachycardia can be found in healthy subjects.[15 16 38] Two studies in healthy middle-aged men suggest that long-term participation in physical exercise may diminish ventricular extrasystoles.[39 40] The results of Talan *et al.*[21] and those of the present study give some slight support to this notion. The proportion of athletes with ventricular extrasystoles was not different from the proportion of controls with ventricular extrasystoles, but none of the athletes had complex forms.

FINAL COMMENTS

Through the recent widespread adoption of ambulatory electrocardiographic recording, it has become evident that findings traditionally regarded as indicative of heart disease also occur in healthy individuals. Endurance athletes are a group at one extreme of the physiological spectrum, and though variations in the function of sinus and atrioventricular nodes probably arise through prolonged intensive physical training, their true clinical significance will remain obscure until results of long-term prospective studies become available. Sudden death in competitive athletes, a rare event,[41] has in most cases been associated with structural diseases of the heart, hypertrophic cardiomyopathy and coronary anomalies being commonest.[41] Though the latter might cause electrocardiographic abnormalities similar to those reported here, no data available suggest that such abnormalities in the electrocardiograms of athletes predispose to sudden death.

Results of animal studies,[36] the disappearance of all atrioventricular blocks as heart rate increases, and the observation that second degree Wenckebach-type atrioventricular block appears and disappears in accordance with the starting and stopping of vigorous physical training in top athletes[11] support the concept that at least the transient atrioventricular blocks observed in the athletes represent a physiological phenomenon. It must, nevertheless, be borne in mind that, in rare instances in adolescents, frequent

Wenckebach-type second degree atrioventricular block has been reported to progress to complete heart block.[42]

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Cardiac sequelae of acute head injury

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SUMMARY An intensive 72 hour study of the cardiovascular effects of severe diffuse brain injury was made in seven patients. No other major injury was present. Patients received optimal care very rapidly after injury and intracranial pressure, which was continuously monitored, was maintained at or just above normal by elective positive pressure ventilation techniques. Three patients showed evidence of progressive myocardial ischaemia on continuous electrocardiographic monitoring. Two of these patients died. Ventricular arrhythmias were uncommon but one of the patients with ischaemia developed ventricular tachycardia. Heart rate patterns were very abnormal but did not predict complications. Blood pressure did not vary greatly and cardiac outputs were usually normal. Pronounced excesses of urinary catecholamines and serum creatine kinase 2 isoenzyme (CK MB) as well as total creatine kinase were found. Histological evidence of myocardial damage could be shown at necropsy in the one case whose heart was available for study.

This study shows that the cardiac effects of isolated diffuse cerebral injury may be harmful and even fatal despite correction of secondary factors such as anoxia and raised intracranial pressure. The findings suggest that evaluation of the potential benefits of sympathetic blockade is warranted. Cardiac complications of cerebral damage deserve wider recognition by intensive care personnel, neurologists, and neurosurgeons.

Electrocardiographic abnormalities and myocardial damage are recognised accompaniments of subarachnoid haemorrhage.[1-4] The subsequent clinical course of these patients may be complicated by rebleeding, investigation and surgery, and occasional diffuse cerebral ischaemia. Intervention designed to protect the heart may therefore have no effect on the overall prognosis. Myocardial damage after cerebral trauma has received less attention, and no systematic attempt has been made to examine potential cardiac sequelae of head injury alone. All such patients, except those with acute haematomata, show a neurological deficit that is maximal initially, but can be expected to improve steadily with appropriate clinical care. Many of these patients can make an excellent neurological recovery. A group of young subjects with no prior history of cardiac disease who had sustained an isolated severe head injury in road accidents was therefore studied to determine whether any serious cardiac sequelae resulted.

Patients and methods

We studied seven patients with severe head injuries from road accidents. Their ages ranged from 11 to 39 (mean = 22). All had been apparently in perfect health before their accident. None was overtly obese or in any other way abnormal, with the exception of their presenting injury. Questioning of relatives disclosed no evidence of prior cardiac disorder, hypertension, or other significant disease. The presence of any other injury excluded patients from the study.

Computerised axial tomographic scans of the brain were obtained in all cases. The presence of a focal lesion or haematoma also excluded patients from the study. All patients were deeply unconscious and showed either no response to pain or purposeless or decerebrate response. Pupils were dilated and fixed to light in all but two. All were admitted immediately to our unit from the scene of the accident. This was usually within the hour but was in all cases less than four hours. Each patient was then studied intensively for 72 hours.

Patients were admitted to the intensive care unit, intubated electively, and ventilated to maintain Pco_2

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in the range 3 to 4 kPa (23 to 30 mmHg). Subdural pressure transducers (Gaeltec Ltd.) were inserted through a burr hole. Continuous recording of the electrocardiogram was made with an Oxford-Medilog recorder and was analysed using an Oxford analysis system and a Reynolds Pathfinder. Recordings were continued for 72 hours. A thermodilution cardiac output catheter was sited in the pulmonary artery and used for pressure monitoring and regular measurements of cardiac output. Routine pulse and blood pressure measurements were made by the nursing staff. Daily assays of creatine kinase (CK) and its myocardial isoenzyme (CK MB) were made from serum samples. Care was taken to avoid possible enzyme degradation[5 6] and isoenzyme separation was then achieved by electrophoresis on agarose gel. A fluorimetric technique was used to measure enzyme activity.[7 8] Twenty-four hour urine samples were collected for assay of free catecholamines and their metabolites.[9–11] On each of the first three days in hospital, the Pco_2 was allowed briefly to rise to normal and cerebral blood flow to both hemispheres was measured using a ^{133}Xe rebreathing method.[12 13] No parasympatholytic drugs were used in management. The maintenance of a satisfactory intracranial pressure by ventilatory techniques meant that none of these patients received corticosteroids or hyperosmolar fluids. Paralysis for ventilation was achieved with pancuronium alone, other drugs being unnecessary by virtue of the patient's deeply unconscious state.

Written consent could not be obtained for this plan of management and investigation but the objectives of such intensive care and monitoring were discussed with the relatives in all cases and approval was obtained for each patient. The 11-year-old child was not, however, exposed to ^{133}Xe or subjected to Swan-Ganz catheter insertion.

Results

NEUROLOGICAL FINDINGS

All patients had severe diffuse brain injury without any focal lesion as evidenced by computerised axial tomographic scanning. In consequence cerebral blood flow was low bilaterally in all cases but rose steadily throughout the 72 hour period of observation, from a mean value of 33·4 ml/100 g tissue per min to 40·8 ml/100 g per min ($p<0·001$ by paired t test; normal value for this group of patients 51·5 ml/100 g brain tissue per min[13]). Intracranial pressure on day 1 varied from a mean minimum pressure of 21·6 cm H_2O to a mean maximum pressure of 26·4 cm H_2O. No significant change occurred on the subsequent days of study (upper limit of normal 18 to 20 cm H_2O). The absolute range was 18 to 30 cm H_2O and no intervention was deemed necessary to reduce pressure apart from reduction of Pco_2 by ventilation.

CARDIOVASCULAR FINDINGS

Blood pressure in the adult patients varied between 110/70 and 205/110 mmHg (lowest recorded in the 11 year old child 60/40 mmHg). Typically, values were normal or slightly raised. Mean cardiac outputs were slightly above normal (6·2 l/min on day 1, with no significant change on days 2 or 3). These were influenced, however, by one patient who consistently showed outputs above 10 l/min.

12 lead electrocardiograms showed features associated with intracerebral lesions.[14] Peaked P waves and T waves were seen, with short PR intervals in two cases. Definite ischaemic change of the ST segment was only present, however, in one case on routine electrocardiogram (inferior lead ST depression) and this resolved in later tracings.

Continuous tape recording of the electrocardiogram disclosed very abnormal patterns. A normal heart rate trend recording in a resting subject is shown in Fig. 1. By contrast, the typical pattern in our patients was of a pronounced sinus tachycardia without any beat to beat variation (Fig. 2). This was present in five cases on day 1. Heart rate pattern generally became more normal, but one case showed sudden accelerations of heart rate on day 2, with dramatic variation in sinus rate from around 75/min to 160/min (Fig. 3).

Continuous electrocardiographic monitoring disclosed evidence suggestive of significant myocardial ischaemia (ST segment depression of 3 mm, 5 mm, and 13 mm) in three cases. One patient showed steadily increasing depression of the ST segment with concomitant increase in heart rate (Fig. 4). Peak heart rate of 190/min and ST depression of 13 mm were seen. Despite treatment with beta-blocking agents during the later hours after admission, lethal cardiac arrhythmias supervened (Fig. 5). Another patient had salvoes of ventricular tachycardia on day 1 and had developed 5 mm ST depression on day 3. This patient died suddenly on day 5 after making apparently satisfactory neurological progress. Histological study of the heart showed focal myocardial necrosis. Study of the brain and other organs did not show a clear cause for death. With the exception of the patient with ventricular tachycardia, ventricular arrhythmias were infrequent. Isolated ventricular premature beats occurred in an unpredictable fashion, were generally fewer than 30/hour, and were transient.

BIOCHEMICAL FINDINGS

Twenty-four hour urinary catecholamines were raised in all cases (Table 1). Metabolites were frequently raised but to a lesser degree. CK levels showed pronounced variation but were frequently grossly high.

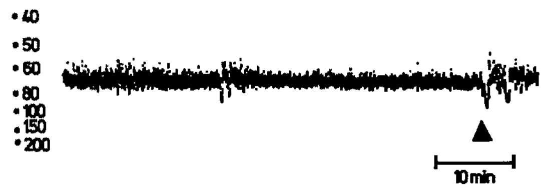

Fig. 1 *One hour heart rate trend in normal adult, obtained by plotting electrocardiogram R-R interval from a continuous 24 hour recording. Ordinate: instantaneous heart rate. Abscissa: time; time marker indicates 10 minute period. One hour where the subject is resting in bed is shown. The subject falls asleep after about half an hour. At arrow, first episode of rapid eye movement sleep occurs. Compare Fig. 2 and 3 (see text).*

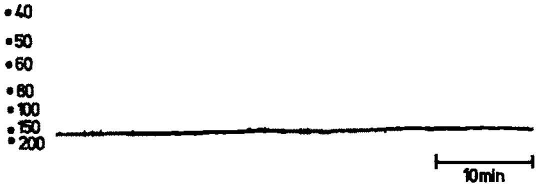

Fig. 2 *Case 2. One hour heart rate trend on first day after acute head injury. Scale as in Fig. 1. Note unvarying sinus tachycardia, mean rate 158/min.*

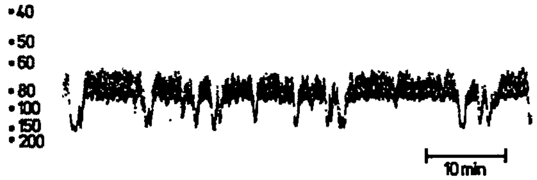

Fig. 3 *One hour heart rate trend on second day in patient who initially showed cardiac rhythm similar to the case in Fig. 2. Note abrupt and extreme accelerations in heart rate.*

CK MB levels were also raised (Table 2). CK MB is not detectable in normal subjects in our laboratory, but there is controversy over methodology in this field. Conditions which have provoked rises in total CK have produced small increases in CK MB. Significant rises in CK MB have been observed in cardiac injury only (*vide infra*).

Discussion

Little or no mention of cardiac sequelae after head injury is made in current neurosurgical texts. This study provides evidence that young and healthy subjects who suffer an isolated severe head injury are at risk from secondary myocardial damage, despite optimal conventional management. Our study differs in several important respects from previous reports suggesting myocardial injury in these circumstances[15 16]. Firstly, patients studied were all admitted directly to a neurosurgical unit immediately after their injury. No patient underwent inter-hospital transfer. Very early direct admission under neurosurgical care is unusual in the United Kingdom[17] and these patients received optimal treatment very rapidly. Intensive care and controlled hyperventilation were instituted on admission, thus minimising secondary effects of anoxia and raised intracranial pressure. Intracranial pressure monitoring was used to establish the efficacy of this treatment. In addition, care was taken to exclude from the study any patients with possible pre-existing cardiac disease, and computerised axial tomography

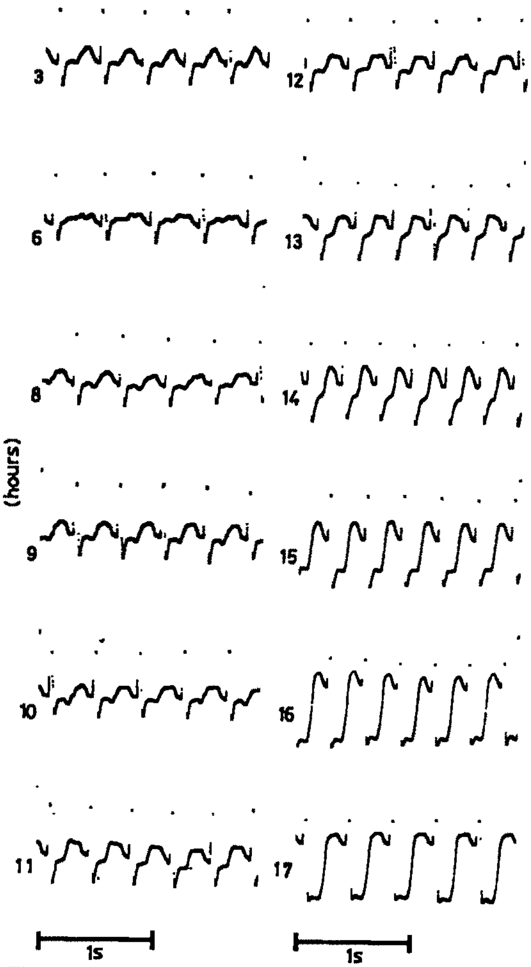

Fig. 4 *Extracts taken from 24 hour electrocardiogram in the case whose heart rate trend is shown in Fig. 2. Each extract is taken at the end of the hour indicated. Heart rate increases from 150/min to 190/min. ST segment becomes depressed in hour 9 and reaches 13 mm below isoelectric line in hour 17.*

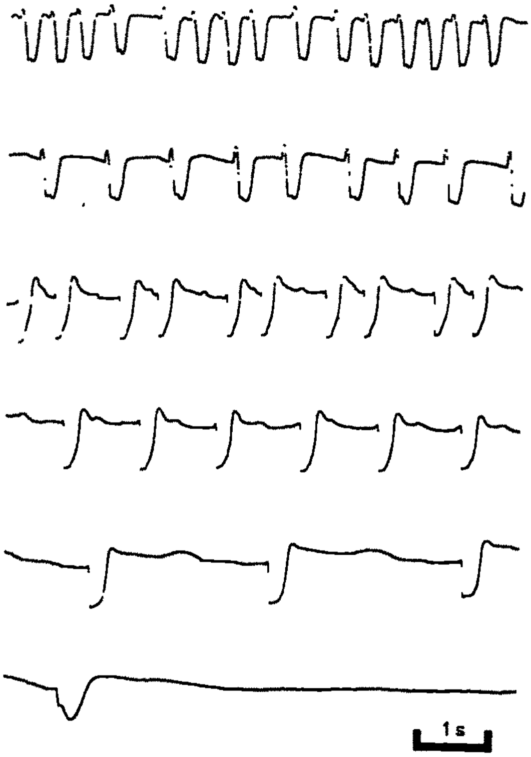

Fig. 5 *Terminal arrhythmias during hour 18 in patient discussed in Fig. 2 and 4.*

scanning was used in all cases to exclude patients with focal lesions such as haematomata. Patients with additional major injury were also excluded. The effects studied were thus those which were caused by diffuse cerebral injury itself.

The evidence for cardiac morbidity and mortality in these patients rests on several investigative methods. Firstly two patients died, and neither from any apparent intracranial cause. In the one heart which was available to us for study, focal myocardial necrosis was found. We have observed similar changes after subarachnoid haemorrhage[18] and several studies suggest that catecholamines are the major determinant of such lesions.[19-22] Similar findings can be observed after catecholamine infusion and in phaeochromocytoma.[23] The harmful effects may further be potentiated by corticosteroids.[24]

There is controversy over two of the other study methods used in the investigation of these patients: namely, the findings on continuous electrocardiographic recordings, and the results of total CK and isoenzyme CK MB assays. Poorly understood electrocardiographic changes are common in cerebral injury[25] but the findings of ST segment depression to the extent shown here—3 mm, 5 mm, and 13 mm are less well recognised. The second and third patient both showed very high catecholamine levels. Such extreme sympathetic stimulation may produce gross changes in regional myocardial perfusion[26] and result in myocardial damage. This is probably partly because of vasoconstriction since angiotensin under appropriate conditions may also provoke such changes.[27] The additional metabolic energy demand produced by sympathomimetic amines may, however, have its own deleterious effect. The inotropic action of these agents may be mediated secondarily by enhanced delivery of intracellular calcium and this accumulation may increase ischaemic damage.[28] The resultant effects on the electrocardiogram are less well understood. Emotion, stress, and sudden pressure loading may all provoke electrocardiographic abnormalities in subjects whose coronary arteries are normal.[29-31] Some of these effects may be duplicated by catecholamine infusions and can be returned to normal by beta-blockade. There is evidence to support both a cellular electrophysiological effect,[32] or an action on blood flow redistribution[26] as a mechanism for this observation. The very gross changes seen in case 2, however, in the presence of entirely satisfac-

Table 1 *Levels of catecholamines and their metabolites in 24 hour urine collections; presence of pronounced sinus tachycardia and ST segment depression is also noted*

Case No.	*Age (y)*	*Sex*	*ST depression*	*Heart rate >150 at any time*	*Day 1*				*Day 2*				*Day 3*			
					Adr	*Nor*	*HMMA*	*META*	*Adr*	*Nor*	*HHMA*	*META*	*Adr*	*Nor*	*HMMA*	*META*
1*	39	F	Yes	Yes	330	3340	71	3·6	670	1050	68	2·1	630	1670	63·5	3·6
2†	22	M	Yes	Yes	2080	5070	59·5	5·2	—	—	—	—	—	—	—	—
3	11	M	No	Yes	260	1305	44·5	3·5	625	2040	44	4·6	—	—	—	—
4	27	M	Yes	No	—	—	—	—	1500	2025	69	5·2	955	3540	73	6·2
5	21	M	No	No	780	500	33	1·7	1790	495	45	3·2	1500	490	54	5·6
6	16	M	No	No	1120	2170	52	6·8	1065	845	48	5·6	1290	1460	40	5·1
7	19	M	No	Yes	1225	1370	18·5	1·4	1815	9030	44·5	3·7	1700	3850	35·5	3·8

Adr, adrenaline, nmol, normal range 0 to 275 nmol/24 h; Nor, noradrenaline, nmol, normal range 110 to 1100 nmol/24 h; HMMA, 4-hydroxy-3-methoxy-mandelic acid, µmol, normal range 10 to 35 µmol/24 h; META, combined metanephrines, µmol, normal range 0 to 4 µmol/24 h.
*Patient died on fifth day.
†Patient died on first day.

Table 2 *Levels of creatine kinase; values of total CK given in IU/l (normal < 130); isoenzyme CK MB given in % of total CK (normally undetectable)*

Case No.	*Day 1*		*Day 2*		*Day 3*	
	Total CK	*MB%*	*Total CK*	*MB%*	*Total CK*	*MB%*
1*	8750	4	8950	3·1	1070	1·2
2†	—	—	—	—	—	—
3	60	1·6	290	2·0	—	—
4	—	—	1050	4·0	3100	4·0
5	500	2·7	780	3·2	360	2·6
6	1720	4·7	1110	6·5	—	—
7	430	3·6	490	3·4	530	4·4

*Patient died on fifth day.
†Patient died on first day.

tory blood gases, plasma electrolytes, and intracranial pressure, together with an extreme and unwavering sinus tachycardia suggest that real and lethal cardiac ischaemia was present until terminal arrhythmias developed. In case 1 a lesser degree of ST segment depression was seen, but ventricular tachycardia during tape recordings and sudden death on the fifth day after admission, combined with necropsy evidence of focal myocardial necrosis all indicate that ischaemic cardiac damage occurred.

The heart rate trend recordings in our patients suggest that sympathetic overactivity is common early after severe brain injury, and this accords with the measured urinary catecholamines and their metabolites. The two patients who died had the highest levels. Overactivity may not be constant, however, and bizarre cyclical discharges as seen in Fig. 3 may occur. We have attempted to correlate these findings with the release of CK MB isoenzyme of CK. As yet no perfect method for fractionation of CK isoenzymes exists[33 34] and this has confused the published reports on this subject. Some authors have considered CK MB as "cardiospecific"[35–37] but low levels which may reach 2% total CK have been found in normal subjects and in a variety of non-cardiac disorders.[38] Recently evidence has been presented for differing lability of the isoenzymes, and modifications in collection methods which we have adopted have been suggested to avoid oxidative changes which may alter electrophoretic mobility.[5 39] Further study on subsequent head injury cases has shown the presence of "brain specific" isoenzyme (CK BB) in a number of patients, and satisfactory separation between this and CK MB has been achieved. We have attempted to rule out the effects of skeletal trauma as a cause of enzyme rises in our subjects by studying separately a series of 10 patients undergoing major orthopaedic surgery. In these patients total CK did not exceed 600 IU/l and CK MB remained at 2% or less. Thus, though there is some overlap, there is apparently release of myocardial CK in our patients. Kaste and his colleagues have provided evidence that this occurs[15] and may worsen prognosis. Some of their cases included purely intracranial catastrophes where there could be no question of skeletal muscle injury.

The results of our study, and of other attempts to investigate the damaging effect of brain lesions on the heart,[15] suggest that attention to the cardiovascular system may be important in neurosurgical practice. Further investigation is needed to explore the possibility that the heart can be protected against the damage induced by intense sympathoadrenal stimulation. A second study has therefore been initiated to investigate the possible protective effects of cardioselective beta-blockade. Non-selective beta-blockade is theoretically unattractive by virtue of a potentially unopposed alpha-vasoconstrictor action in resistance vessels resulting in systemic hypertension. Preliminary studies suggest that accurate titration may be difficult to achieve, however; plasma adrenaline and noradrenaline levels have been found in excess of 18 times the upper limit of normal values by the present authors (unpublished observations).

Our findings may also be relevant in the field of cardiac transplantation which has re-emerged as an occasional treatment for advanced cardiovascular failure in the United Kingdom. Many donor hearts are removed from victims of road accidents, and by extrapolation from our results some of these may have microscopic foci of myocardial necrosis. Even if there is no lasting impairment of cardiac function, myocardial necrotic lesions may have some effect on the immune response in the recipient.

In conclusion, in a series of patients with isolated diffuse cerebral injury who had no prior cardiac defect, who were admitted rapidly to hospital, and who were intensively monitored and treated to reduce unnecessary metabolic or respiratory insults, evidence of extreme sympathetic disturbance with deleterious cardiac sequelae was found. Our studies suggest that a large proportion of these cases may show biochemical evidence of disturbance of catecholamine mediators, and secondary release of CK and CK MB from injured tissue, some of this arising from the heart. Electrocardiographic evidence of severe disturbance may be found. Direct evidence of myocardial damage may be apparent in patients who die. Attempts must now be made to interrupt the damaging stimulus-response link in these patients. Cardiac morbidity and possible mortality deserve wider attention from those working in intensive care or neurosurgical units.

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Abnormal Q waves in right sided chest leads provoked by onset of right bundle-branch block in patients with anteroseptal infarction

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SUMMARY In five cases of anteroseptal myocardial infarction complicated by intermittent right bundle-branch block, the onset of right bundle-branch block provoked the appearance of abnormal Q waves in leads V1 and V2, whereas a small initial R wave was present in the same leads during normal conduction. The intermittency of the conduction disturbance indicated that the Q waves were "right bundle-branch block dependent". It was also apparent that right bundle-branch block shifted the electrical location of the infarct towards the right, and made it look much larger. Right bundle-branch block dependent Q waves may arise during the acute stage of an anterior infarct suggesting, fallaciously, that an acute extension has occurred, or during the chronic stage, leading to the erroneous supposition that a new infarct has developed. The abnormal Q waves of anteroseptal infarction complicated by fixed right bundle-branch block, though obviously related to the infarct, may be dependent on the right bundle-branch block.

In some patients with anteroseptal myocardial infarction, we have observed that the onset of right bundle-branch block may cause the appearance of abnormal Q waves in leads V1 and V2, by turning an rS pattern into a QR. Though the septal involvement becomes more readily apparent, the mere occurrence of right bundle-branch block may give rise to erroneous diagnosis of a new infarct or an extension of a previous one. Five cases showing this electrocardiographic sign are presented in this paper, and four previously reported cases[1–3] are reviewed.

Case reports

CASE 1

A 48-year-old man had suffered an acute anterior wall myocardial infarction complicated by intermittent right bundle-branch block 10 months previously. Fig. 1 shows the full conventional electrocardiogram with right bundle-branch block. In the lower strip, two postextrasystolic beats disclose a normally conducted QRS in which a small initial R wave can be seen, whereas the right bundle-branch block beats were all characterised by the presence of a deep Q

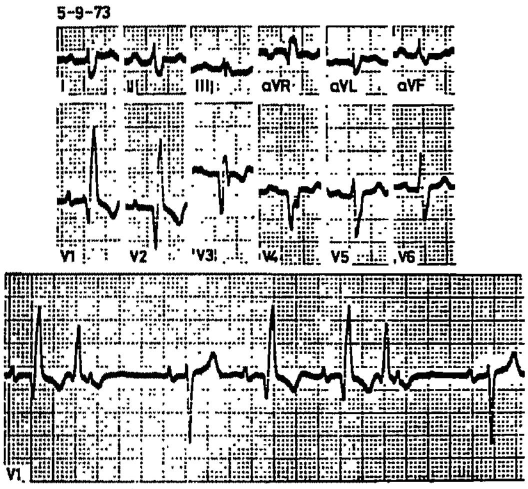

Fig. 1 *Case 1, 10 months after the acute episode. Right bundle-branch block and anterior myocardial infarction. Lower strip shows the appearance of right bundle-branch block dependent Q waves in lead V1.*

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wave. It was apparent that the Q wave in V1 was right bundle-branch block dependent. Fig. 2 shows two electrocardiograms recorded during the acute stage, illustrating that at that time the Q wave occurred both with or without right bundle-branch block. The R wave in V1 (during normally conducted beats) was first seen to occur several months after the acute episode, suggesting that tissue somewhere in the infarcted area had recovered from the ischaemic process. The patient died four years later because of recurrent pulmonary embolism. A routine necropsy showed an old transmural anterior and septal myocardial infarction. The right ventricular free wall was not involved.

CASE 2

A 50-year-old man developed an acute anterior wall myocardial infarction and intermittent right bundle-branch block. Four electrocardiograms were selected (Fig. 3) to illustrate that Q waves occurred in leads V1 to V4 only when right bundle-branch block was present (B and D), while a small R wave appeared in the same leads when right bundle-branch block was absent (A and C). Right bundle-branch block conveyed the impression that the infarct was larger and that its electrical location was shifted towards the right. Though transient additional ischaemic injury causing both the right bundle-branch block and the Q waves cannot be totally excluded, such a possibility is less likely than the simple occurrence of right bundle-branch block dependent Q waves, because disappearance of the right bundle-branch block was repeatedly and instantaneously followed by reappearance of R waves. Subsequently the patient developed left bundle-branch block, paroxysmal atrioventricular block, and recurrent ventricular tachycardia, and died on the eighth day. No necropsy was obtained.

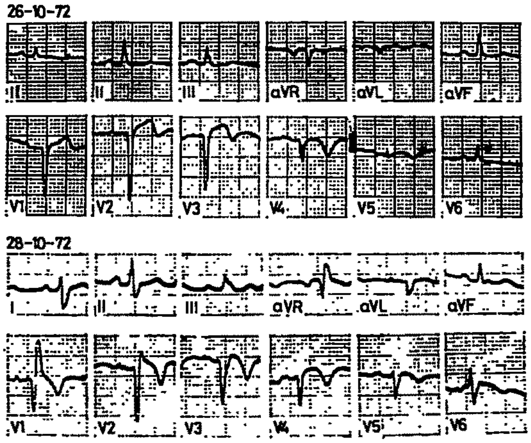

Fig. 2 *Case 1, during the acute stage of an anterior myocardial infarction. At this time Q waves are seen in the normal conducted as well as in the right bundle-branch block beats.*

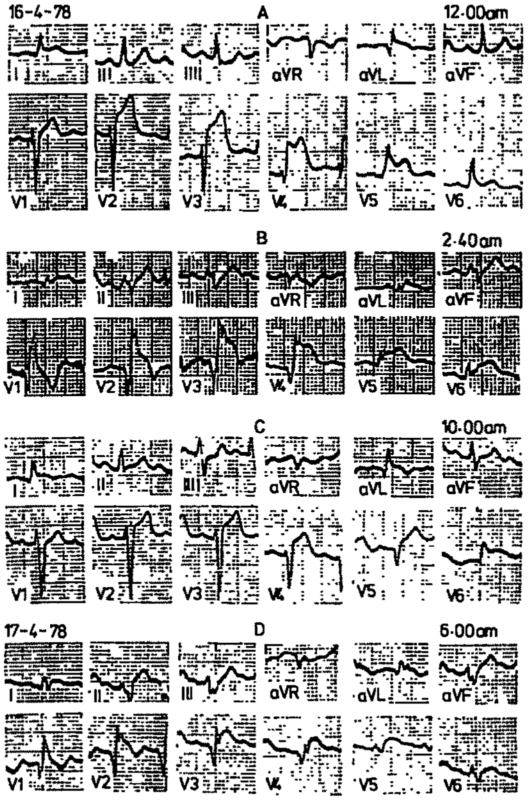

Fig. 3 *Case 2, during the acute stage of an anterior myocardial infarction. Abnormal Q waves in leads V1 to V4 are clearly seen only when right bundle-branch block is present (B and D). When the right bundle-branch block disappears (A and C) those Q waves are replaced by conspicuous R waves.*

CASE 3

Fig. 4 shows four electrocardiograms recorded from an 81-year-old woman within the space of six hours. There is an acute anterior myocardial infarction with left anterior hemiblock, and right bundle-branch block occurs in the second electrocardiogram but not in the first and third tracings. During right bundle-branch block abnormal Q waves appear in leads V1 to V5 but not in leads I, aVL, and V6. Conversely, a small R wave is seen in V1 to V3 and Q waves occur in I, aVL, and V6 when right bundle-branch block is absent. Right bundle-branch block produces abnormal Q waves in right sided chest leads and "shifts the infarct towards the right", simulating an acute extension. The fourth electrocardiogram shows that even a small degree of incomplete right bundle-branch block evoked the right bundle-branch block dependent Q

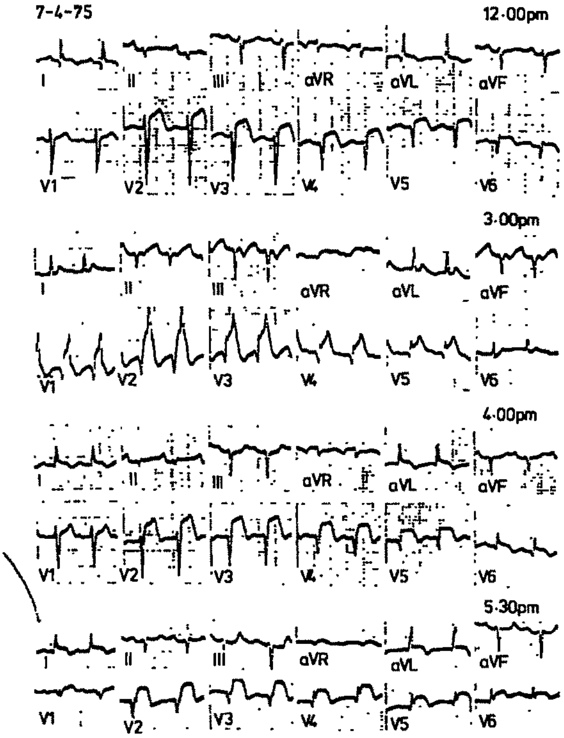

Fig. 4 *Case 3. The four electrocardiograms were taken during the acute stage of an anterior infarction. Complete (second ECG) as well as incomplete right bundle-branch block (fourth ECG) produces Q waves in the precordial leads V1 to V5.*

waves. The patient died in cardiogenic shock three hours later. Necropsy showed total obstruction of the anterior descending coronary artery close to its origin and an acute transmural myocardial infarction involving the anterolateral wall of the left ventricle and nearly the entire ventricular septum. The right ventricle was spared.

CASE 4

A 39-year-old man had suffered an acute anteroseptal myocardial infarction. The first tracing obtained 48 hours after the acute episode showed right bundle-branch block, left anterior hemiblock, and abnormal Q waves in leads V1 to V3. A second electrocardiogram, 24 hours later, showed disappearance of the right bundle-branch block which coincided with restoration of a small R wave in V1 to V3 and more conspicuous Q waves in I and aVL. A third electrocardiogram was recorded three years later. Without any further episode of chest pain, right bundle-branch block had recurred and was again accompanied by abnormal Q waves in V1 to V3, while Q was absent from I and much smaller in aVL. In a previous publication,[4] this was interpreted as indicating the development of a new anteroseptal infarct complicated again by right bundle-branch block. It seems now more likely, however, that what the patient actually developed was right bundle-branch block, which elicited the "new" Q waves and the apparent shift of the infarct towards the right.

CASE 5

The three electrocardiograms in Fig. 5 were recorded from a 61-year-old man 34 hours after a prolonged episode of retrosternal pain. The tracing at 1700 hours shows right bundle-branch block, left anterior hemiblock, and abnormal Q waves in V1 to V2, denoting an anteroseptal infarction. A QS in III and aVF is compatible with involvement of the inferior wall. At 1430 and 1710 hours right bundle-branch block was absent and initial R waves were present in V1 to V6. It should be noted that frank ST segment elevation did not occur in any of the electrocardiograms, so that in the absence of right bundle-branch block the anterior infarct was not clearly apparent. The next day the patient developed left bundle-branch block followed shortly by complete atrioventricular block and died on the third day. Necropsy disclosed a massive anterolateral, inferior, and septal myocardial infarction (Fig. 6). The entire septum was necrotic but for a small subendocardial rim on the right below the pars membranacea. Careful study of many histological sec-

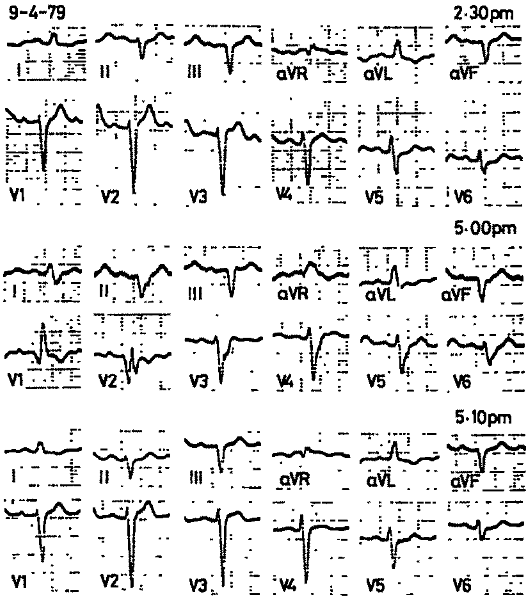

Fig. 5 *Case 5. The three electrocardiograms were recorded during an acute coronary episode. Q waves denoting an anteroseptal infarction are only seen when right bundle-branch block is present.*

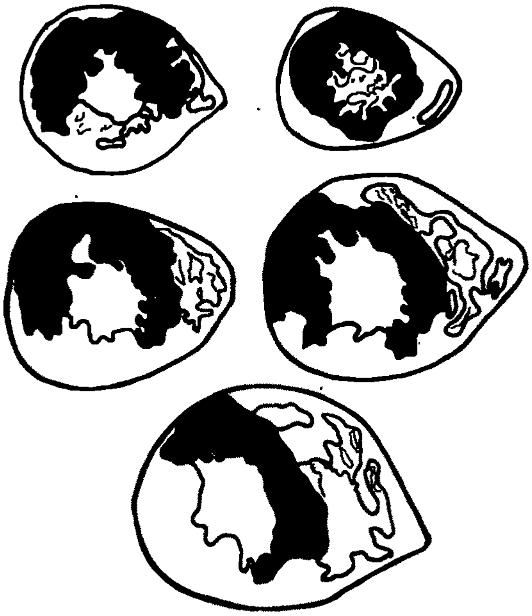

Fig. 6 *Case 5. Necropsy findings. Serial sections of the heart showed a massive anterolateral inferior and septal myocardial infarction, without any right ventricular involvement (in black necrotic areas).*

tions failed to show any evidence of right ventricular involvement.

Discussion

MECHANISM OF RIGHT BUNDLE-BRANCH BLOCK DEPENDENT Q WAVES

For many years it has been acknowledged that right bundle-branch block does not alter the direction of the early QRS forces.[1] This depends on the fact that septal activation takes off from the left septal surface[4 5] because of earlier arrival of the impulse coming down the left bundle-branch.[6] Accordingly, Q waves tend to disappear in left bundle-branch block, and do not change (or do not occur if previously absent) in right bundle-branch block. Though disputed by some,[7-9] the many cases of intermittent right bundle-branch block and left bundle-branch block reported by various authors,[4-10 11] show this mechanism to be true under a wide variety of clinical conditions. The five cases presented in this paper are an exception to the rule, and the fact that the occurrence of right bundle-branch block dependent Q waves was related to anterior and septal myocardial infarction suggests that the mechanism was probably similar in all of them. In our cases initial R waves in V1 and V2 were present during normal conduction but not during right bundle-branch block, suggesting that they represented activation of part of the heart "served" by the right bundle-branch, probably the thin anterior wall of the right ventricle. We postulate that a transmural septal infarction cancelled out the normal septal force and made it possible for a small normally ineffectual electrical force of right ventricular origin to become apparent as a small R wave in V1 and V2, and that right ventricular infarction would make this phenomenon less likely to occur. This hypothesis is supported by the fact that in our three patients who were examined at necropsy septal infarction was transmural and right ventricular involvement was absent, and by the evidence that anteroseptal infarcts usually fail to extend to the right ventricle.[12] Under such conditions, the abnormal Q waves in V1 and V2 may only occur if right bundle-branch block is present. Though left anterior hemiblock occurred in four of our cases, it was unrelated to the Q waves in V1 and V2. In case 1 the Q waves occurred without left anterior hemiblock; in cases 2 and 4 right bundle-branch block elicited the Q waves both in the presence or absence of left anterior hemiblock; and in cases 3 and 5 the Q waves were absent during isolated left anterior hemiblock and only occurred when right bundle-branch block appeared. In addition, no other known form of fascicular block was apparent in the electrocardiograms showing the abnormal Q waves. An alternative explanation would be a transient myocardial injury causing both the right bundle-branch block and the Q waves. In fact, it has been reported that Q waves may occur only transiently during acute episodes of coronary insufficiency.[13-16] This was not the case, however, in case 1, in whom right bundle-branch block was intermittent under chronic conditions; it was unlikely in cases 2 and 5, in whom right bundle-branch block dependent Q waves were seen to occur on different occasions; but cannot be totally excluded in cases 3 and 4. An incomplete left bundle-branch block may justify the occurrence of small R waves in V1 and V2 even in the presence of a septal infarct, and under such conditions right bundle-branch block may suppress those R waves. Though this latter mechanism may eventually be operative in other cases, it did not seem to participate in the present series, with the possible exception of case 5.

ROLE OF RIGHT VENTRICLE

A normally activated right ventricle is a necessary condition for the occurrence of initial R waves in V1 and V2 in the presence of a transmural septal infarction and, as a consequence, for the occurrence of right bundle-branch block dependent Q waves. This does not explain, however, the cases in which an anteroseptal myocardial infarction causes abnormal Q waves either with or without right bundle-branch block. For example, in case 1 the Q waves were not right bundle-branch block dependent during the acute stage (Fig. 2), and it was only when the small R waves reappeared in the chronic stage (Fig. 1) that the Q waves became right bundle-branch block dependent. In fact, if the small R waves which disappear during right bundle-branch block are of right ventricular origin, their absence during normal conduction must necessarily suggest some right ventricular involvement. It is then reasonable to assume that in anteroseptal myocardial infarction in general, a QS in V1 and V2 may indicate additional right ventricular damage, and reappearance of the R waves may suggest recovery of a tissue which because of its anatomical features (the much thinner wall) or peculiarities of its blood supply[12] may more readily survive from the ischaemic insult than the septum and left ventricle. This possibility, which requires more precise anatomical studies for confirmation, finds support in the studies by Myers *et al.*[17 18] showing that large anterior and septal infarcts may, though not often, involve the anterior wall of the right ventricle.

INCIDENCE OF RIGHT BUNDLE-BRANCH BLOCK DEPENDENT Q WAVES

Right bundle-branch block dependent Q waves may be more common than previously suspected. In 1962 Szilagyi and Ginsburg[2] reported a case under the title of "Acute myocardial infarction revealed in the presence of right bundle-branch block". In a classic paper by Wilson *et al.*[1] a case of anterior infarction complicated by transient right bundle-branch block is illustrated (their Fig. 19), showing that Q waves in leads V1 to V4 were present during right bundle-branch block, while a small R wave occurred during normal conduction. The authors pointed out that the "small initial R waves . . . apparently represent activation of the free wall of the right ventricle". Two examples of right bundle-branch block dependent Q waves were reported by Gambetta and Childers,[3] though they interpreted the "rate-dependent right precordial Q waves" as a manifestation of "septal focal block". In one of the patients late reappearance of right bundle-branch block led to readmission to hospital because a new infarct was simulated. More important than the individual cases which require intermittency of the right bundle-branch block to be unveiled is the fact that anterior infarction complicated by right bundle-branch block is almost invariably accompanied by abnormal Q waves in V1 and V2[1] while uncomplicated anteroseptal infarction commonly displays small R waves in the same leads. In a study by Myers *et al.*,[19] 12 of 20 necropsy proven cases of anteroseptal infarction showed small R waves in V1 and V2. Of course, it may be argued that the Q waves more readily seen in the presence of right bundle-branch block are simply the result of a larger infarct. Though this may certainly be so, the fact remains that in an unknown number of cases of anterior infarction with right bundle-branch block the abnormal Q waves in V1 and V2 may depend to a great extent on the right bundle-branch block.

CLINICAL IMPLICATIONS

In some cases of anteroseptal myocardial infarction the diagnosis can only or more readily be made in the presence of right bundle-branch block. Right bundle-branch block seems to "expand and shift the infarct towards the right". Since this phenomenon occurs in association with large anteroseptal infarcts, it may be said that right bundle-branch block conveys a more correct impression of the extension of the infarct. During the acute stage the onset of right bundle-branch block may incorrectly suggest an extension of a recent anterior myocardial infarction. In the chronic stage the occurrence of right bundle-branch block may cause Q waves to appear in V1 and V2 and lead to an erroneous conclusion that a new infarct has developed. These are the most important mistakes that can be incurred by overlooking the electrocardiographic sign discussed in this paper.

We are indebted to Dr Jose Milei for the anatomical study performed on case 5.

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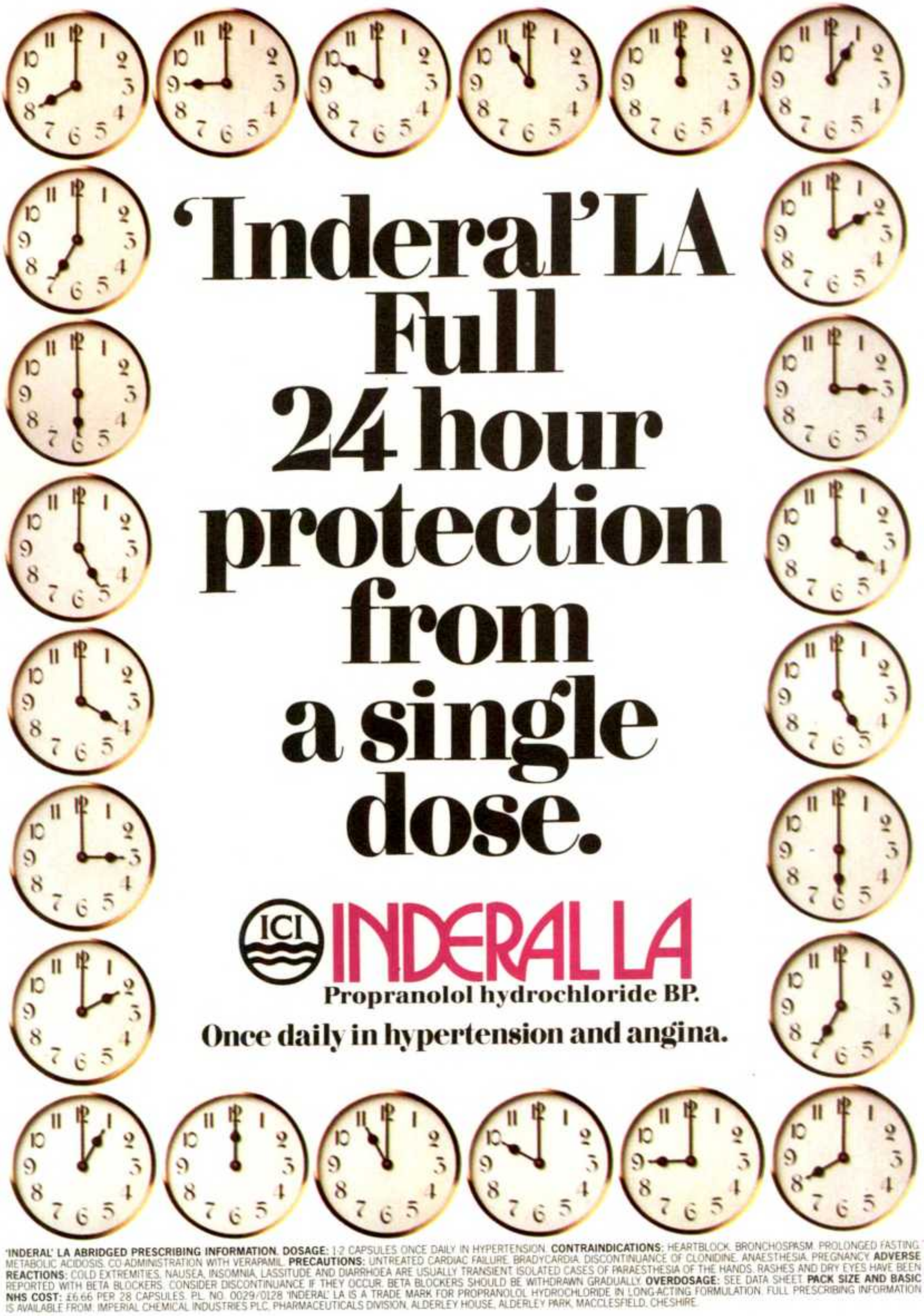

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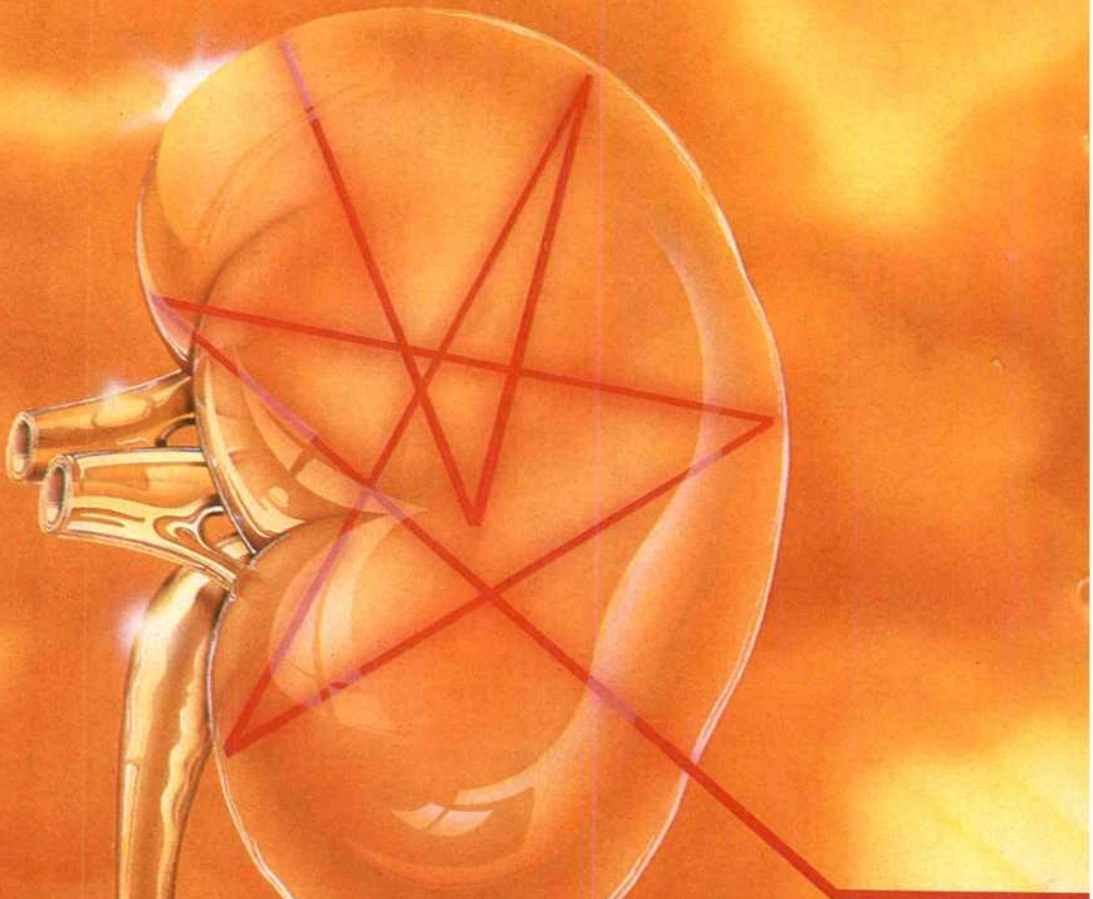

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Creatinine Clearance (ml/min 1.73 m^2)	Dosage Interval (Hours)
>75	8
75-35	12-24
34-20	24-48
19-8	48-72
7-5	72-108 (3 to 4.5 days)

When concomitant diuretic therapy is required, a loop diuretic (e.g. frusemide) is preferable to a thiazide diuretic.

Children Safety and effectiveness in children have not been established. Starting dose should be 1 mg per Kg bodyweight up to a maximum of 6 mg per Kg bodyweight divided into three doses per day. **CONTRA-INDICATIONS, PRECAUTIONS AND WARNINGS:- Contra-Indications** Previous hypersensitivity to Capoten **Warnings** NEUTROPENIA/AGRANULOCYTOSIS and PROTEINURIA have been reported in patients receiving Capoten. Urinary protein should be checked (dip stick) prior to treatment, monthly for 8 months and periodically thereafter. WBC should be carried out prior to treatment, fortnightly for three months and periodically thereafter. **Hypotension** A precipitous reduction of blood pressure may occasionally occur within the first three hours following the initial dose of Capoten in patients on diuretics, on a low sodium diet or undergoing dialysis. An exaggerated hypotensive effect may also occur with one or two subsequent doses. Medical supervision should be maintained for one hour after the initial dose. This transient hypotensive response is not a contra-indication to further doses which can be given without difficulty once blood pressure has increased after volume expansion. **Hypotension in Patients with Severe Congestive Heart Failure**. These patients, having either normal or low blood pressure, may experience marked falls in blood pressure, which have on rare instances been associated with arrhythmia or conduction defects, after the first few doses of Capoten. Because of the potential fall in blood pressure in these patients, therapy must be started in the hospital. Patients should be followed closely for the first two weeks of treatment and whenever the dose of Capoten and/or diuretic is increased. Patients treated for severe congestive heart failure should be warned to increase their physical activity slowly. **Serum Potassium** Since Capoten decreases aldosterone production, elevation of serum potassium may occur, especially in patients with renal failure. Potassium sparing diuretics or potassium supplements, if needed, should be used with caution, since they may lead to a significant increase in serum potassium. **Changes in Renal Function** Some patients with renal disease, particularly those with renal artery stenosis, have developed increased serum concentration of BUN and serum creatinine after reduction of blood pressure with Capoten, usually along with a diuretic. Capoten dosage reduction and/or discontinuation of diuretic may be required. For some of these patients, it may not be possible to normalise blood pressure and maintain adequate renal perfusion. **Pregnancy** The safety of Capoten in pregnancy has not been established. **Nursing Mothers** Exercise caution. **Surgery/Anaesthesia** In patients undergoing major surgery, or during anaesthesia with agents which produce hypotension, Capoten will block angiotensin II formation secondary to compensatory renin release. This may lead to hypotension which can be corrected by volume expansion. Capoten may cause a false-positive urine test for acetone. **Side Effects** Neutropenia/Agranulocytosis Proteinuria see Warnings. Skin rashes and taste disturbance have been reported. Gastric irritation and abdominal pain may occur. **Other** Paraesthesias of the hands, serum sickness, cough, bronchospasm and lymphadenopathy have been reported. Hypotension – see Warnings. Tachycardia has been observed in a few volume depleted patients. **Overdosage** In the event of overdosage, hypotension would be the most important problem. Volume expansion with an intravenous infusion of normal saline is the treatment of choice for restoring the blood pressure to normal. Capoten is removed by dialysis. **PACKAGE QUANTITIES** in bottles of 100. **Basic NHS Price** 25 mg tablets 100 – £21.40. **PRODUCT LICENCE NUMBERS, NAMES AND ADDRESSES Product Licence Numbers** Capoten tablets 25 mg PL 0034/0193;
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Product Licence Holder E.R. Squibb & Sons Limited, Squibb House, 141/149, Staines Road, Hounslow, Middlesex, TW3 3JA. **Legal Category** POM **Date of Preparation** November 1981. Capoten is a Squibb Trademark.
▼ Special reporting to CSM required.

REFERENCES

1. The Lancet 1980; 2: 108–110
2. The Lancet 1980; 2: 105–107
3. J Roy Soc Med 1981; 74: 357–362

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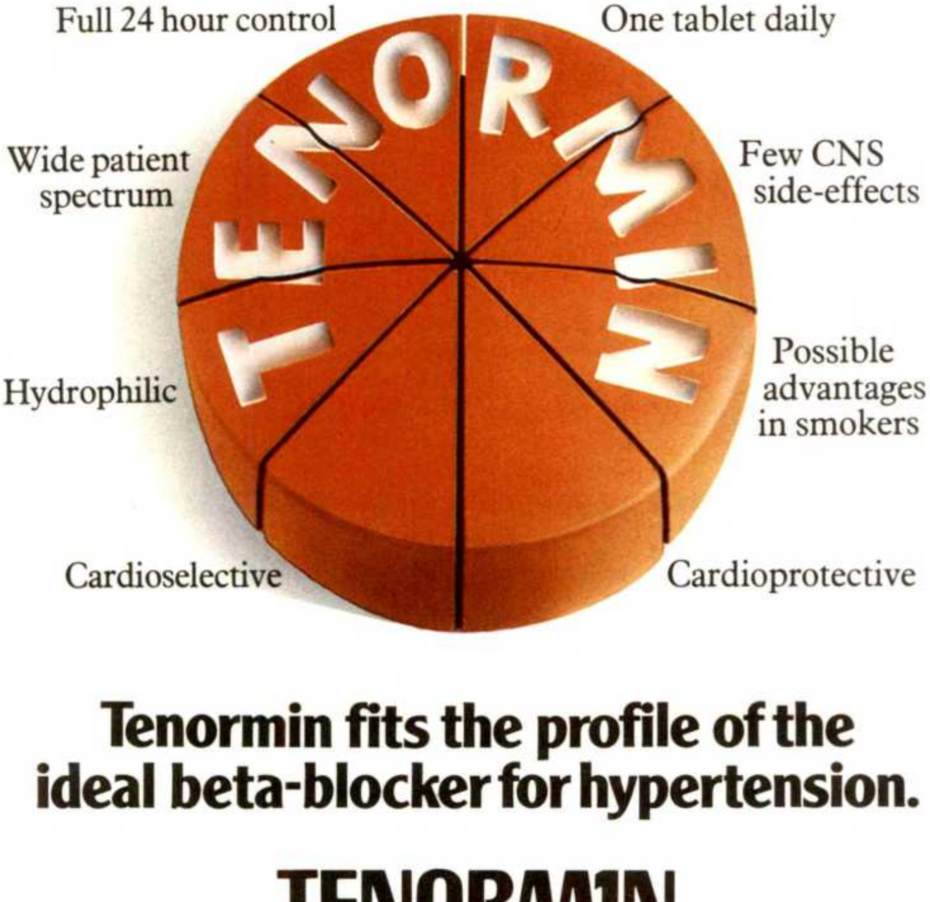

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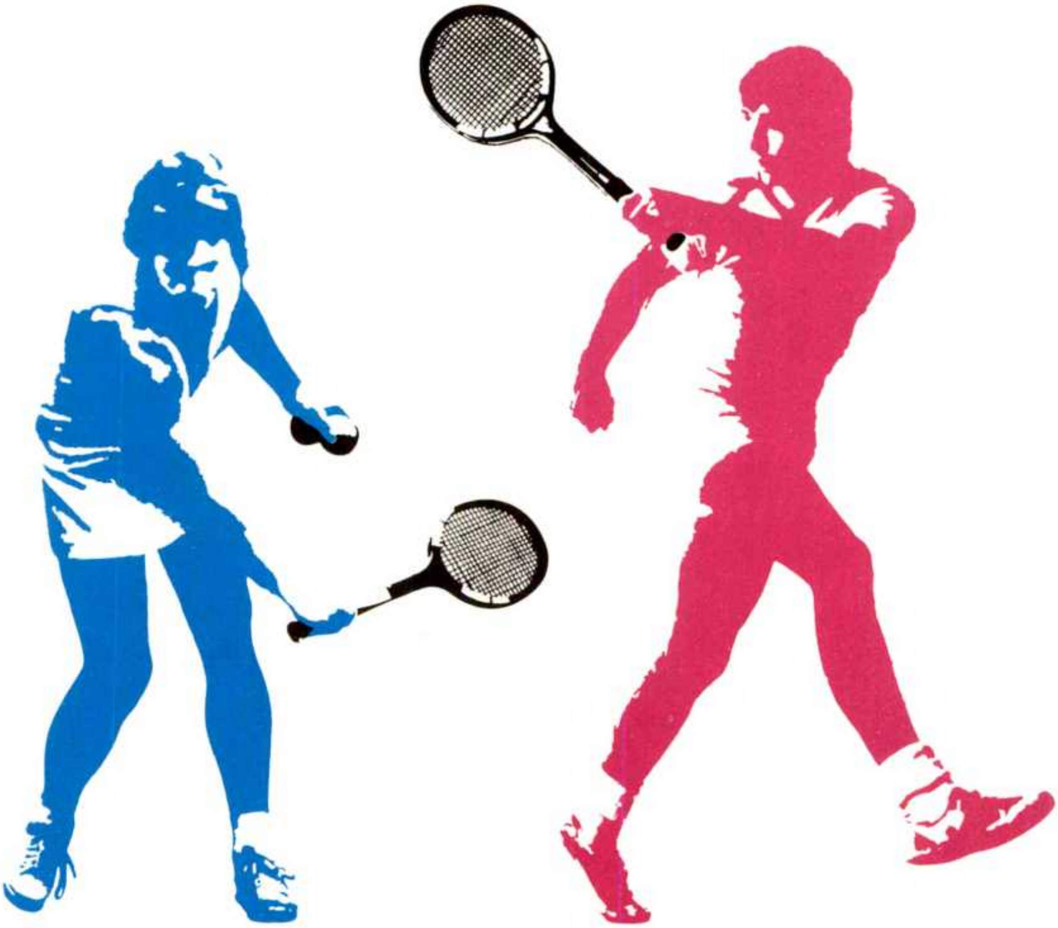

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Br Heart J 1982; **47**: 233–8

Haemodynamic and myocardial metabolic effects of captopril in chronic heart failure

KANU CHATTERJEE, JEAN-LUCIEN ROULEAU,* WILLIAM W PARMLEY

From the Cardiovascular Division of the Department of Medicine and the Cardiovascular Research Institute, University of California, San Francisco, California, USA

SUMMARY In 15 patients with chronic left ventricular failure caused by ischaemic heart disease, cardiac output and right heart pressures were measured before and after the oral angiotensin-converting enzyme inhibitor, captopril, which was administered in increasing doses. In 12 of 15 patients, coronary blood flow, and in 11 patients myocardial oxygen extraction and consumption and lactate extraction were also determined before and after captopril therapy. Cardiac index and stroke volume index increased by an average of 25% and 27%, respectively. Pulmonary capillary wedge pressure also decreased in all patients (average 27%), suggesting improved left ventricular function. The rate-pressure product, coronary blood flow, and myocardial oxygen consumption decreased significantly; in one of 11 patients there was myocardial lactate production, despite decreased myocardial oxygen demand and consumption. These findings suggest that in patients with chronic heart failure, improved left ventricular function with captopril is generally associated with decreased metabolic cost and that deterioration of metabolic function occurs infrequently.

That angiotensin-converting enzyme inhibitor, captopril, is a potent antihypertensive agent is well established.[1 2] Recently, improvement of left ventricular function and amelioration of symptoms of heart failure with captopril have also been documented in normotensive patients.[3–8] Thus, captopril appears to have a potential role for the long-term management of patients with chronic heart failure.

Although beneficial haemodynamic effects of captopril are observed in most patients, little information is available regarding its effects on coronary circulation. In many patients, ischaemic heart disease is the underlying aetiology of chronic heart failure. The evaluation of changes in coronary haemodynamics and myocardial metabolism is particularly relevant in this subset of patients. The purpose of this study, therefore, is to assess not only changes in left ventricular function, but also changes in coronary haemodynamics and myocardial metabolism with captopril in patients with chronic heart failure resulting from ischaemic heart disease.

Subjects and methods

Fifteen patients with congestive heart failure of more than two months' duration formed the patient population. All patients were male and their ages ranged from 46 to 70 years. All patients had at least one documented myocardial infarction; all 15 patients had electrocardiographic evidence of anterior myocardial infarction. Four of 15 patients had selective coronary arteriography and all four had severe triple vessel coronary artery disease.

At the time of the study, all patients had clinical evidence of biventricular failure with pulmonary artrial hypertension. Chest x-ray fims showed significant cardiomegaly in all patients. Two-dimensional echocardiograms and/or radioangiograms showed the presence of a dilated, poorly contracting left ventricle in all 15 patients. Ten patients were in New York Heart Association Class III, and five were in Class IV heart failure at the time of the study.

All vasodilator drugs were discontinued at least four days before the study. Digoxin and diuretics were continued and given every evening after completion of the study. After obtaining written consent, a triple lumen balloon flotation catheter was placed in the pulmonary artery percutaneously via the right subclavian vein. Right atrial pressure, pulmonary artery pressure, pulmonary capillary wedge pressure, and cardiac output by thermodilution (triplicate) were determined with this balloon flotation catheter.[9] For measurement of coronary sinus flow and for obtaining coronary sinus venous blood samples, a No. 8 thermodilution coronary sinus flow catheter (Wilton

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*Dr Rouleau is a recipient of the McLaughlin Fellowship from McGill University School of Medicine, Canada.

Accepted for publication 24 August 1981

Webster Co., California) was placed in the coronary sinus percutaneously via the left subclavian vein. In order to minimise coronary sinus reflux, the catheter was positioned under fluoroscopy near the great cardiac vein.[10] Arterial pressure was recorded directly by cannulating the radial artery.

Coronary sinus flow was measured by the constant infusion thermodilution technique.[11] Coronary sinus flow was calculated by the formula:

$\left(\frac{Tb - Ti}{Tb - Tm}\right) \times 1{\cdot}08 \times 46$ ml/min, where Tb = temperature of blood, Ti = temperature of mixture of blood and the injectate, 1·08 = a constant accounting for specific heart and density of both blood and injectate, 46 ml/min is the injection rate of the injectate. Arterial and coronary sinus venous blood samples were drawn simultaneously for the determination of oxygen saturation, O_2 content, and lactate concentration. The lactate concentration was measured using the enzymatic fluorometric method of Loomis,[12] and the oxygen (O_2) saturations were measured using a Corning 175 automated blood and pH analyser.

The haemodynamic and metabolic variables were calculated as follows:

Cardiac index (CI), l/min per m^2 = cardiac output/body surface area; stroke volume index (SVI), ml/m^2 = CI/HR, where HR = heart rate; stroke work index (SWI), g m/m^2 = SVI × (MSP-PCWP) × 0·0136, where MSP = mean systolic pressure and PCWP = mean pulmonary capillary wedge pressure.

Systemic vascular resistance (SVR), dynes s cm^{-5} = (MAP-RAP)/CO × 80, where MAP = mean arterial pressure, RAP = mean right atrial pressure.

Myocardial oxygen extraction (Art − CSO_2), volume % = arterial O_2 − coronary sinus O_2 content.

Myocardial O_2 consumption (MVO_2), ml/min = coronary sinus flow × (Art − CSO_2) × 10^{-2}.

Myocardial lactate extraction (% lactate) =

$$\frac{\text{Arterial-coronary sinus}}{\text{Arterial}} \text{ Lactate (mg)} \times 100.$$

CAPTOPRIL ADMINISTRATION

After the insertion of the catheters, patients were allowed to rest for one hour, and two sets of control measurements were obtained 15 minutes apart, before oral administration of captopril. Our previous experience[5] suggested that significant hypotension may occur in some patients if the initial dose of captopril is 25 mg. Therefore, in this study, a smaller (2·5 mg) dose was given initially, and then the dose was increased to 6·25, 12·5, 25, 50, 100, and 150 mg every two hours until there was a 10 mmHg fall in mean arterial pressure. In individual patients, the next larger dose was not given when a fall in arterial pressure was noted with the previous smaller dose. All 15 patients tolerated 2·5 and 6·25 mg doses; in one patient, the dose could not be increased after 6·25 mg, in four after 12·5 mg, and in nine after 25 mg. In only one patient could the dose be increased to 50, 100, and 150 mg. Measurements of systemic and coronary haemodynamics and metabolic variables were repeated two hours after each dose. Throughout the study period care was taken to ensure that the coronary sinus catheter remained in the same position by repeated fluoroscopy and injection of contrast medium.

STATISTICAL ANALYSIS

Paired analysis between control and the peak effects of captopril for each variable was performed using the paired "t" test. When the effects of different doses were compared, a two-way analysis of variance was done using the Student-Newman-Keuls test.

Results

Because only one patient received a dose larger than 25 mg, the haemodynamic and metabolic effects of 50, 100, or 150 mg dose of captopril were excluded when the dose response effects were analysed. The average haemodynamic and metabolic response to 2·5, 6·25, 12·5, and 25 mg oral doses of captopril are summarised in Table 1. After a 2·5 mg dose no appreciable changes in haemodynamics were observed in any of the 15 patients. After a 6·25 mg dose, mean arterial pressure fell, and after 25 mg, there was a 18% decrease in mean arterial pressure. There was a gradual decrease in systemic vascular resistance, and it fell by 30% after the 25 mg dose. Cardiac index increased by an average of 20% after the 25 mg dose. Stroke volume index also increased in all but one patient. There was also a significant fall in pulmonary capillary wedge, right atrial, and pulmonary arterial pressures. Changes in stroke work index were variable and were not statistically significant.

Heart rate tended to decrease with increasing doses of captopril, though the average changes did not reach statistical significance. The product of peak systolic pressure and heart rate (rate-pressure product), however, decreased significantly, and after the 25 mg dose there was an average decrease of 15%. Coronary sinus flow and myocardial oxygen consumption were determined in 12 of the 15 patients, and myocardial oxygen consumption and lactate extraction were determined in 11 patients. Coronary sinus flow and myocardial oxygen consumption also tended to decrease with increasing doses of captopril. As not every patient received all the doses of captopril, however, and as in individual patients the peak effects were observed after different doses, the average changes in coronary sinus flow and myocardial oxygen consumption after each dose did not reach statistical significance. There was a tendency to decreased

Table 1 *Systemic haemodynamic response (mean ±SD) to increasing doses of captopril in patients with chronic heart failure*

Captopril dose (mg)	0	2·5	6·25	12·5	25
Heart rate (beats/min)	80±15	81±13	80±14	79±11	78±12
Mean arterial pressure (mmHg)	82±10	78±10	75±9***	71±11**	67±12**
Pulmonary capillary wedge pressure (mmHg)	24·3±5·3	23·4±7·7	22·3±8·0	21·7±8·3	19·7±7·6***
Right atrial pressure (mmHg)	12±6	12±6	11±5	11±5	11±5
Cardiac index (l/min per m²)	2·0±0·5	2·0±0·5	2·1±0·5	2·2±0·5	2·4±0·5***
Stroke volume index (ml/m²)	26±8	26±8	27±7	29±8	31±9***
Stroke work index (g m/m²)	30·5±14	29·0±13·3	29·6±12·1	30·6±15·7	30·0±13·9
Systemic vascular resistance (dynes cm−⁵)	1552±397	1506±718	1380±311	1189±274*	1078±295***
Peak systolic pressure times heart rate (mmHg/min×10⁻³)	10·2±2·3	9·8±2·0	9·4±2·2	8·8±2·2***	8·2±2·3**
Coronary sinus flow (ml/min)	63·2±21·6	60·5±24·4	57·8±23·3	59·2±27·8	60·2±28·7
Lactate extraction (vol %)	35±16	36±17	40±18	35±15	34±29
Myocardial oxygen consumption (ml/min×10⁻²)	12·7±2·0	12·7±1·9	12·8±1·8	12·4±1·9	12·1±2·1

*p=<0·05, **p=<0·001, ***p=<0·005.

myocardial oxygen extraction after 12·5 and 25 mg doses, and the average myocardial lactate extraction remained unchanged.

The peak haemodynamic effects in individual patients occurred after different doses of captopril. The peak haemodynamic effects of captopril were defined when the mean arterial pressure fell by at least 10 mmHg. The average changes in the peak systemic and coronary haemodynamics and in metabolic variables are summarised in Table 2, and illustrated in Fig 1, 2, and 3. The peak haemodynamic effects were characterised by a significant decrease in mean and diastolic blood pressures, heart rate, and systemic vascular resistance. Cardiac index and stroke volume index increased significantly by an average of 25% and 27%, respectively. There was also a distinct fall in pulmonary capillary wedge pressure (Fig 1). Improvement in left ventricular function was indicated by the concomitant increase in cardiac and stroke volume indices and decrease in pulmonary capillary wedge pressure (Fig. 2).

The product of peak systolic pressure and heart rate (rate-pressure product) decreased significantly, and there was also a concomitant decrease in coronary sinus flow and myocardial oxygen consumption (Fig. 3). Myocardial oxygen extraction decreased slightly, and this decrease in Art-CSO$_2$ was the result of an increase in coronary sinus O$_2$ content. The average transmyocardial lactate extraction remained unchanged. The relation between the changes in rate-pressure product and coronary sinus flow, and myocardial oxygen consumption in individual patients, is illustrated in Fig. 4. In all patients rate-pressure product decreased and coronary sinus flow decreased in 11 of the 12 patients. Myocardial O$_2$ consumption also decreased in 10 of the 11 patients. Thus, in almost all patients improved left ventricular function was associated with decreased metabolic cost. There was myocardial lactate production in only one of 11 patients, and in the other 10 patients lactate extraction remained unchanged.

Discussion

That angiotensin-converting enzyme inhibitor, captopril, produces beneficial haemodynamic effects in patients with chronic heart failure has been documented in many previous studies.[3-8] In the present study, a similar beneficial haemodynamic

Table 2 *Peak haemodynamic and metabolic effects (mean ±SD) of captopril in chronic heart failure*

	No. of patients	*Control*	*Captopril*	*Probability*
Heart rate (beats/min)	15	80±15	75±12	0·01
Mean arterial pressure (mmHg)	15	82±10	64±10	0·001
Diastolic arterial pressure (mmHg)	15	61±10	47±8	0·001
Pulmonary capillary wedge pressure (mmHg)	15	24·2±5·3	17·6±5·1	0·001
Cardiac index (l/min per m²)	15	2·0±0·5	2·5±5·1	0·001
Stroke volume index (ml/m²)	15	25·7±8·0	32·7±7·0	0·001
Peak systolic pressure times heart rate (mmHg/min×10⁻³)	15	10·2±2·3	7·6±1·9	0·001
Coronary sinus flow (ml/min)	12	63·2±21·6	55·8±24·7	0·025
Myocardial O$_2$ extraction (vol %)	11	12·7±2	12±2	0·025
Myocardial O$_2$ consumption (ml/min)	11	8·2±2·8	6·6±3·1	0·025
Myocardial lactate extraction (%)	11	35±16	38±20	NS

NS=not significant.

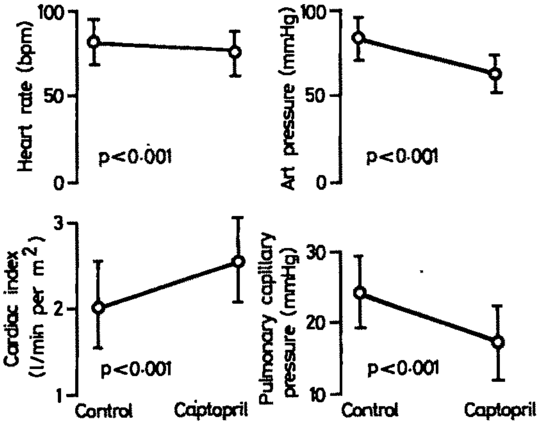

Fig. 1 *Changes in heart rate, mean arterial pressure, cardiac index, and pulmonary capillary wedge pressure at peak effect of captopril. Heart rate, arterial pressure, and pulmonary capillary wedge pressure decreased and cardiac index increased.*

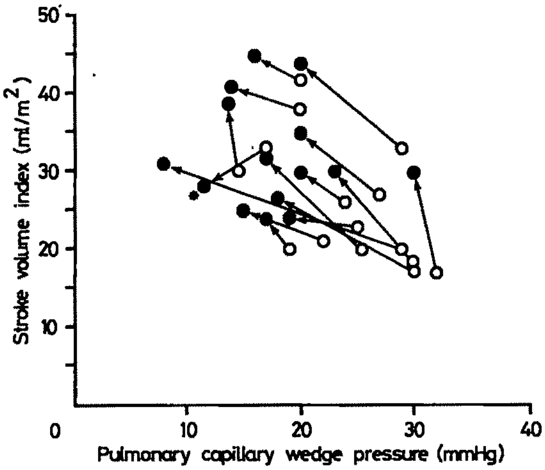

Fig. 2 *Changes in stroke volume index (vertical axis) and pulmonary capillary wedge pressure (horizontal axis) during captopril treatment. Open circles* (O) *indicate control values; solid circles are values obtained at time of peak effect of captopril; and arrows indicate changes after administration of captopril. In all but one patient* (*)*, stroke volume index increased, along with a decrease in pulmonary capillary wedge pressure, indicating improved left ventricular function.*

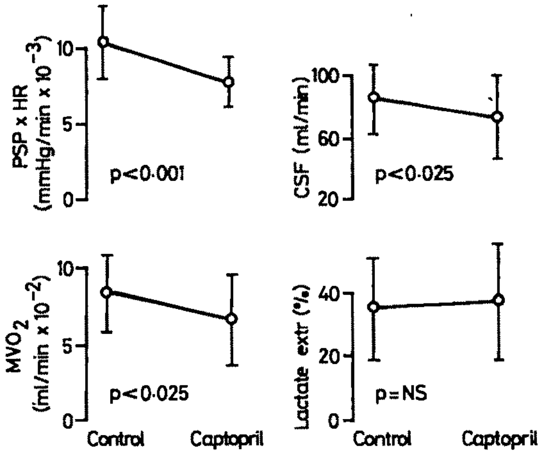

Fig. 3 *Changes in rate-pressure product* ($PSP \times HR$)*, coronary sinus flow* (*CSF*)*, myocardial oxygen consumption* (MVO_2)*, and myocardial lactate extraction at peak effect of captopril. Rate-pressure product, coronary sinus flow, and myocardial oxygen consumption decreased, while lactate extraction remained unchanged.*

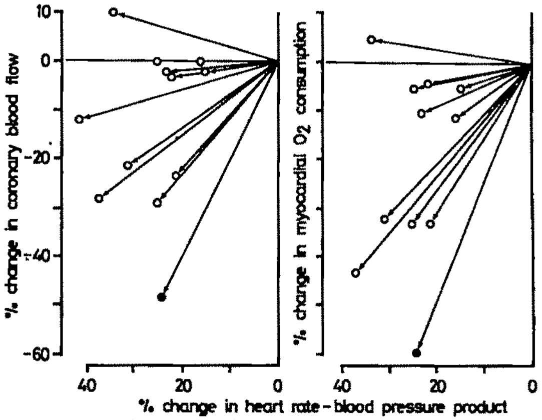

Fig. 4 *Relative changes in rate-pressure product (horizontal axis) and coronary blood flow and myocardial oxygen consumption (vertical axis) in individual patients at peak effect of captopril. The rate-pressure product decreased in all patients and coronary blood flow and myocardial oxygen consumption also decreased concurrently. The one patient who had myocardial lactate production is identified by the closed circle.*

response was obtained. In all patients, an increase in cardiac output and stroke volume, with a decrease in pulmonary capillary wedge pressure was observed, indicating enhanced left ventricular function. The mechanism of improvement in left ventricular function with captopril is likely to be related to the reduction of left ventricular outflow resistance, as systemic vascular resistance and arterial pressure fell in all patients. A pronounced reduction of right atrial and pulmonary capillary wedge pressures was also observed in many patients; such a decrease in systemic and pulmonary venous pressures may be partly the result of venodilatatory effects of captopril, which have been shown by plethysmographic studies.[8] Angiotensin-II is a potent arteriolar constrictor, and the inhibition or attenuation of the effects of angiotensin-II by the converting enzyme inhibitors is likely to be associated with decreased arteriolar tone and systemic vascular resistance. Thus, with captopril, reduction of left ventricular ejection impedance and consequent increase in stroke volume and cardiac output is expected. Angiotensin-II, however, does not appear to cause any direct venoconstriction.[13] Therefore, the venodilatation with captopril is likely to be the result of a mechanism other than the inhibition of the effects of angiotensin-II. Increased activity of the kinin peptides and decreased level of circulating norepinephrine have been observed after administration of converting enzyme inhibitors. Withdrawal of sympathetic venoconstrictor tone, therefore, is a possible mechanism of venodilatation with angiotensin-converting enzyme inhibitors. Whatever the mechanisms may be, reduction in pulmonary and systemic venous pressures with captopril are helpful for the relief of symptoms related to systemic and pulmonary venous hypertension. Pronounced hypotension occurring after the first dose of captopril has been observed in some patients in previous studies. In the present study, the initial dose of captopril was much smaller and the dose was gradually increased. With this dose titration, sudden pronounced hypotension could be avoided, though blood pressure fell in all patients. It appears, therefore, that during the initiation of captopril treatment in patients with normotensive heart failure, dose titration, starting with a smaller dose, is preferable to avoid sudden pronounced hypotension.

The present study also suggests that captopril consistently decreases myocardial oxygen demand and consumption. In all patients, the rate-pressure product, a commonly used index of myocardial oxygen demand, decreased. Changes in left ventricular diastolic volume were not directly determined in our patients. In all patients, however, there was a pronounced decrease in pulmonary capillary wedge pressure which should be associated with decreased left ventricular diastolic volume. As systolic arterial pressure decreased concomitantly, left ventricular wall stress, another major determinant of myocardial oxygen demand, must have declined during captopril treatment. As well as the decreased myocardial oxygen demand, there was also a decrease in myocardial oxygen consumption which was primarily caused by decreased coronary blood flow. In animal studies angiotensin-II has been shown to cause sustained vasoconstriction of the large conductance vessels, and a transient vasoconstriction of the smaller resistance vessels.[14] Attenuation of the effect of angiotensin with captopril, and the possible decrease in angiotensin-induced vasoconstriction, therefore, might be expected to preserve autoregulation. In such circumstances, coronary blood flow is largely influenced by the changes in myocardial oxygen demand. The present study suggests that with captopril, coronary blood flow and myocardial oxygen consumption are predominantly governed by the changes in the haemodynamic determinants of myocardial oxygen demand.

In this study, in most patients there was no change in transmyocardial lactate extraction. In one patient, however, there was myocardial lactate production indicating myocardial ischaemia. In previous studies, lactate extraction of 5% or less has been regarded as evidence of myocardial ischaemia.[15] Using this criterion, in one other patient, myocardial ischaemia might have been precipitated during captopril treatment. Recently, however, it has been shown that decreased lactate extraction to 5% or less can occur in normal subjects, and that evidence for lactate production is necessary for the definitive diagnosis of myocardial ischaemia.[16] Whichever criteria are used for the diagnosis of myocardial ischaemia, it is clear that despite improved left ventricular function and decreased metabolic cost, myocardial ischaemia can be precipitated in some patients. In other clinical studies, recurrent episodes of angina during captopril treatment have been observed in occasional patients.[17] The mechanism for lactate production in one patient in this study remains unclear. The rate-pressure product decreased significantly and there was also a pronounced decrease in pulmonary capillary wedge pressure. Thus, lactate production occurred despite a significant reduction in myocardial oxygen demand, thus precipitating an imbalance between myocardial oxygen demand. In this patient, transmyocardial pressure gradient did not change significantly, suggesting that a decrease in subendocardial blood flow was unlikely. It is possible that coronary blood flow decreased in excess of that expected from the decrease in myocardial oxygen demand, thus precipitating an imbalance between myocardial oxygen supply and demand.

The present study suggests that captopril is a potent vasodilator and has the potential to improve left ventricular function in patients with chronic heart failure. Improved left ventricular function with captopril is usually associated with decreased metabolic cost, and myocardial ischaemia occurs infrequently.

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Measurement of serum C-reactive protein concentration in myocardial ischaemia and infarction

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SUMMARY Serum C-reactive protein (CRP) and creatine kinase (CK) MB levels were measured prospectively in patients with definite myocardial infarction, patients with spontaneous or exercise-induced angina, subjects undergoing coronary arteriography, and patients with non-cardiac chest pain. All individuals with infarction developed raised CRP levels and there was a significant correlation between the peak CRP and CK MB values. The CRP, however, peaked around 50 hours after the onset of pain at a time when the CK MB, which peaked after about 15 hours, had already returned to normal. In 20 patients who recovered uneventfully, CRP levels fell, returning to normal about seven days after infarction in four cases who were followed to this point. In eight complicated cases, including four who died within the first 10 days, the CRP level remained high. Angina alone or coronary arteriography did not cause a rise in the CRP or CK MB concentrations. Increased CRP production is a non-specific response to tissue injury and raised CRP levels in cases of chest pain with a normal CK MB indicated a pathological process other than myocardial infarction. Regular monitoring of CRP levels may also assist in early recognition of intercurrent complications occurring after myocardial infarction.

Differential diagnosis of myocardial infarction from other causes of chest pain is a common clinical problem. Even when the diagnosis is established there are many difficult questions such as: recognition of myocardial necrosis in patients with known ischaemic heart disease, recognition of intercurrent complications in the post-infarct period, prognosis in the immediate post-infarct period, and assessment of convalescent infarct patients for discharge from the coronary care unit to the ward, and from ward to home.

C-reactive protein (CRP) is the classical acute phase reactant,[1] the serum level of which has long been known to increase after myocardial infarction.[2–5] Earlier work, using relatively insensitive and semiquantitative assays, suggested that serial measurement of serum CRP levels may be useful in the diagnosis and management of myocardial infarction.[2 3] We have reinvestigated this possibility in a prospective study of well-characterised patients using a precise quantitative assay for CRP, together with measurements of CK MB, the specific myocardial isoenzyme of creatine kinase.[6]

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Patients and methods

The following groups of patients were studied: 33 with definite myocardial infarction on clinical grounds confirmed by electrocardiogram and a rise in CK MB level, seven with severe angina admitted to the coronary care unit with suspicion of infarction but no increase in CK MB, 12 undergoing exercise testing for known or suspected myocardial ischaemia, 11 undergoing coronary arteriography, and five with chest pain of non-cardiac origin. Venous blood samples were obtained from the patients with infarcts or spontaneous angina on admission, then at two to four hour intervals for the first 24 to 48 hours, and subsequently at eight to 12 hour intervals for the next one to four days in 34 patients and up to 10 days in six patients. The patients in other groups were bled before and 24 and 48 hours after exercise testing or arteriography. Serum was separated after clotting for one hour at room temperature and frozen promptly at −20°C. Samples were thawed once only and run in batches to determine the concentration of CRP using a new rapid immunoradiometric assay,[7] and of CK MB using assay kits (EM Diagnostics Ltd, Greenford, Middlesex). The CRP assay provides results on up to 50 samples in one hour with intra- and inter-assay coefficients of variation of 5 to 10%.[7] Among normal healthy subjects 90% have serum CRP levels less than 3 mg/l and 99% are less than 10 mg/l.[8]

Results

SERUM CRP AND CK MB LEVELS IN PATIENTS WITH DEFINITE MYOCARDIAL INFARCTION

All patients with definite myocardial infarction mounted a CRP response and there was a statistically significant correlation between the peak levels of CRP and of CK MB (Fig. 1, Kendall's rank correlation coefficient $\tau=0{\cdot}441$, $p<0{\cdot}001$). Two individuals had relatively modest peak CRP levels. One was a 74-year-old woman in whom temporal arteritis had been diagnosed one year previously and who was on daily prednisolone therapy. The other was a 40-year-old Negro from the West Indies who had no known antecedent disease or treatment. The peak level of CRP occurred later after the onset of pain than did the peak level of CK MB, the mean±SD time to peak being 50·5±23·3 hours for CRP and 14·8±8·6 hours for CK MB. In 20 uncomplicated cases who made a good recovery the CRP concentration fell from its peak within 12 to 24 hours and in four patients who were followed for a sufficient period, it remained at low levels thereafter. In eight cases, however, in whom progress during the immediate post-infarct period was interrupted by cardiac insufficiency resulting from arrhythmias or a low output state the CRP concentration did not return to normal. Four patients who died within the first 10 days all had persistently high or rising CRP levels at the time of death. These observations are illustrated by the cases shown in Fig. 2 and 3.

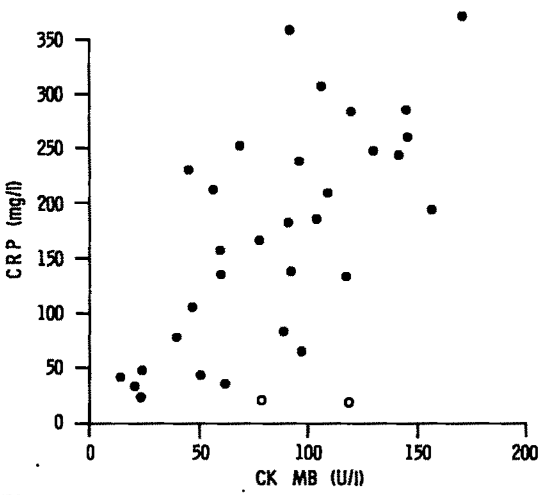

Fig. 1 *Peak serum levels of CRP and CK MB in myocardial infarction. The two individuals with relatively poor CRP response are indicated* (O).

SERUM CRP LEVELS IN ANGINA AND AFTER CORONARY ARTERIOGRAPHY

Among the 12 patients who were studied in relation to exercise testing, six experienced anginal pain during the test and three showed ST segment changes in their electrocardiograms. None showed any rise of either CRP or CK MB. Seven patients with severe chest pain were admitted to the coronary care unit for observation; two of them had crescendo angina. None showed a rise in CK MB though three had modestly raised CRP levels on admission. In only one of these patients did the CRP subsequently increase in concentration, reaching 29 mg/l, and this was a woman of 60 years in whom the original diagnosis of myocardial infarction was revised to pulmonary embolism. She died suddenly but no necropsy was performed. Among the 11 patients undergoing coronary arteriography, lesions were shown in the coronary arteries of eight. The CK MB level did not rise in any case and the CRP rose in only one, from <1 mg/l to 24 mg/l in a subject with normal coronary arteries. Clinical events which occurred during catheterisation but which were not associated with increases in either CK MB or CRP included: an episode of ventricular tachycardia lasting 30 seconds, three episodes of chest pain in three patients, one episode of hypotension, and ST segment/T wave changes in two patients.

SERUM CRP LEVELS IN PATIENTS WITH CHEST PAIN NOT CAUSED BY MYOCARDIAL INFARCTION

Raised CRP concentrations occurred in patients with pulmonary embolism, pneumothorax, and severe chest pain of unknown cause (see below). Furthermore, intercurrent infection or thrombotic complications in patients with angina or after infarction were associated with increased CRP production but no rise in CK MB. This situation is exemplified by the case illustrated in Fig. 4, a man of 60 years known to have ischaemic heart disease. After an episode of angina one month previously he was admitted to the coronary care unit with an episode of severe chest pain. Intravenous and intra-arterial lines were inserted for monitoring and the electrocardiogram was compatible with subendocardial ischaemia. There was no rise of CK MB and the CRP was also initially normal, but about 24 hours after admission it began to rise slowly. After 60 hours he became febrile and then confused but no cause of these symptoms was demonstrable either on clinical or direct microbiological examination. During this time his serum CRP had climbed rapidly to a very high level. Blood and other cultures were taken, the intravascular lines removed, and the broad spectrum antibiotics begun. Over the next 48

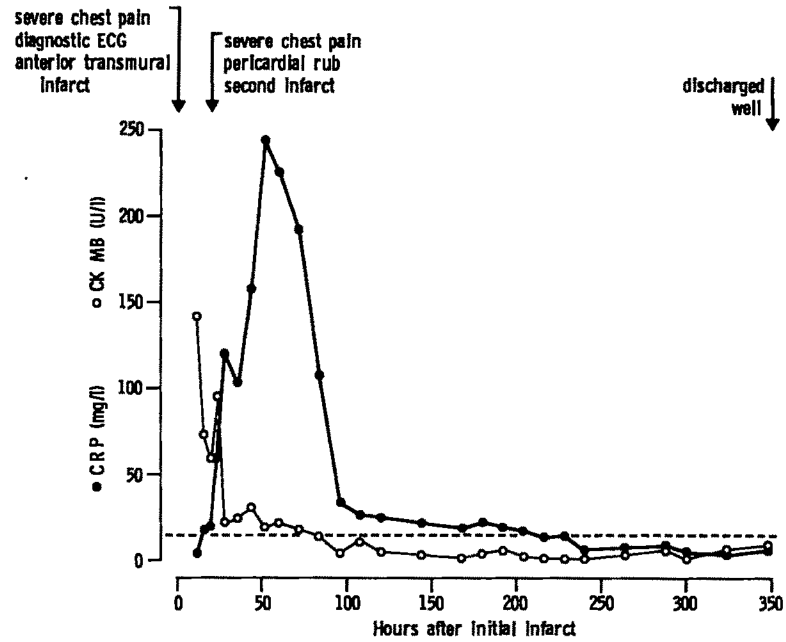

Fig. 2 *Serial CRP and CK MB values in a 52-year-old man who suffered two episodes of myocardial infarction in rapid succession but then made an uneventful recovery.* — — —, *upper limit of normal for CK MB.*

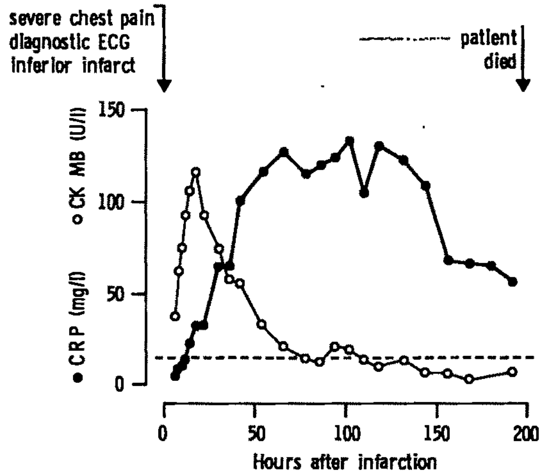

Fig. 3 *Serial CRP and CK MB values in a 50-year-old man who had previously recovered from an anterior myocardial infarct but then suffered fresh inferior infarction. He remained unwell thereafter with a low output state and died 200 hours after the onset of pain.* — — —, *upper limit of normal for CK MB.*

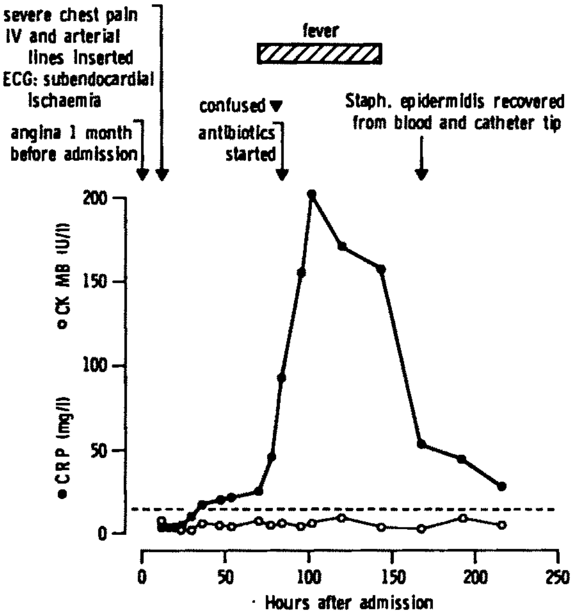

Fig. 4 *Serial CRP and CK MB values in a 60-year-old man with known ischaemic heart disease after acute admission to the coronary care unit with severe chest pain. There was no evidence of infarction but he suffered a septicaemic illness associated with the presence of intravascular lines.* — — —, *upper limit of normal for CK MB.*

hours he improved and became afebrile, the CRP falling promptly towards normal, and he made an uneventful recovery. *Staph. epidermidis* was subsequently grown from the blood and the catheter tip obtained before starting antibiotics.

Another example of the potential value of regular, frequent, and rapid monitoring of CRP is provided by the case of a 37-year-old Indian man who was admitted to hospital with a clinical diagnosis of crescendo angina. The chest radiograph was normal but the electrocardiogram showed slight left ventricular hypertrophy. Over the next 42 hours there was no rise in CK MB, aspartate aminotransferase, or any other routinely measured biochemical variable. A slight fever developed but the pain abated and the patient insisted on discharging himself. He experienced further pain at home during the next few days but refused to be readmitted and he died five days later. Necropsy was refused so the causes of his pain and demise are unknown. Subsequent assay of his serum CRP, however, showed that it rose from a normal value of 2 mg/l on admission to 42 mg/l at 17 hours, 70 mg/l at 28 hours, and 76 mg/l at 42 hours. These high levels indicate unequivocally the onset and progression of a tissue-damaging organic disease process and if available at the time might have assisted in the patient's management or at least facilitated his continued stay in hospital.

Discussion

Increased CRP production is a non-specific response to most forms of cell death, tissue injury, infection, or inflammation, and it is clear that myocardial necrosis is a potent stimulus. All the patients studied here in whom there was a significant rise in CK MB also showed a rise in CRP concentration, and though this was relatively modest in two cases (one of whom was on steroids), there was a significant correlation between the peak values attained by these two completely distinct variables. Similar results have recently been reported in abstract form by Catheline *et al.*[9] Occurrence of the peak level of CRP at a mean time of 50 hours after the onset of pain compared with the peak of CK MB at about 15 hours suggests that measurement of CRP may be useful in cases in which the diagnosis of infarction is only suspected late, or which are only seen for investigation at a time when CK MB has returned to normal.

Cases of spontaneous or induced angina or individuals undergoing coronary arteriography generally did not show an increase of CRP in the absence of a rise in CK MB. Precise sequential measurements of CRP may thus serve as a sensitive test for myocardial necrosis in the context of ischaemic heart disease.

A rise in CRP in cases of chest pain without raised CK MB strongly suggests a non-infarctive or non-cardiac lesion and may assist in diagnosis of the cause of pain or in early recognition of intercurrent complications in cases of angina or after infarction. For example, if the CRP results in the case illustrated in Fig. 4 had been available at the time rather than after the event, cultures could have been taken before the onset of fever or other symptoms, his intravascular catheters changed, and prophylactic antibiotics begun much earlier. Assay of CRP may also provide an objective criterion to assist in decisions regarding suitability of individual patients for transfer from the coronary care unit to the ward or from the ward to home. On all these grounds we suggest that, provided the results are interpreted in the light of detailed knowledge of the patients' clinical condition and in conjunction with CK MB values, regular assay of CRP may play a valuable part in differential diagnosis of the chest pain syndrome and in management of individuals with known or suspected myocardial ischaemia or infarction.

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Acute coronary occlusion during coronary angiography in two cases

Treatment by transluminal disobliteration

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SUMMARY Acute coronary obstruction occurred in two patients during coronary angiography. In one case the obstruction was in the left main coronary artery; in the other it was close to the origin of the left anterior descending artery. In both cases acute cardiac ischaemia ensued, with electromechanical dissociation and collapse, which was not reversible by resuscitation. Rapid disobliteration of the occluded coronary artery was done with a guide-wire pushed through the obstruction via the coronary catheter. The recanalisation was completed by an intracoronary perfusion of streptokinase in one case. In both cases recovery was rapid and spectacular. The occurrence of acute ischaemia during coronary angiography should suggest accidental coronary occlusion. If a thromboembolic origin is suspected, transluminal disobliteration should be attempted. It is simple and can reverse a dangerous condition.

The prevention of acute thromboembolic accidents during arterial catheterisation must be a constant concern of the operator. In the case of selective coronary angiography this risk is increased by the possibility of coronary embolism, the consequences of which can be dramatic: this accident is one of the main causes of death during this investigation.

Despite the experience of our team of 10 years of intensive cardiovascular exploration (with more than 1 000 investigations in 1980 alone), most of the cases including coronary angiography, the "law of series" was such that two coronary obstructions occurred at a few days' interval in our laboratory. In both cases there was acute irreversible shock and this led us to attempt coronary disobliteration according to the technique recently proposed in cases of acute myocardial infarction.[1–3]

Case reports

CASE 1

A 60-year-old woman had a posteroinferior myocardial infarction in September 1979. The persistence of severe angina pectoris led to coronary angiography. The investigation was done on 27 May 1980 by the femoral transcutaneous method. Selective left ventricular angiography, through a pigtail 7 F Cook catheter, showed a ventricular cavity with a normal volume, posteroinferior akinesia, and a contractile anterior wall, ensuring satisfactory ventricular function. The left coronary tree was seen during this injection, but not the right. The catheter was then changed for a Bourassa 8 F left coronary catheter. The coronary ostium was easily reached and was not occluded by the catheter as shown by control of the continuously monitored aortic pressure curve. In the seconds following the first injection, the patient complained of severe thoracic pain while the contrast medium only opacified the first centimetre of the left main coronary, seemingly abutting against an obstacle (Fig. 1a). The electrocardiogram immediately showed major anterior ST segment elevation, followed by extreme bradycardia, cardiovascular collapse, and loss of consciousness. Cardiac massage and other resuscitative measures were begun.

Twenty minutes later the patient's condition was still critical and it was decided to attempt coronary disobliteration with a guide-wire. The catheter was then changed and the left main coronary artery was again reached with another 8 F Bourassa catheter. Glyceryl trinitrate, 2 mg, was then injected into the left coronary artery, but there was no recanalisation on a subsequent angiogram. A straight Teflon guide-wire,

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uncored for the last 8 cm (Cordis J guide, 0·35 mm diameter), was then pushed through the catheter into the left main coronary artery, first into the left anterior descending artery approximately to its mid-course (Fig. 1b), and then into the first 3 or 4 cm of the circumflex artery. The guide-wire was removed a few seconds after its intracoronary insertion and a subsequent injection of contrast medium showed the whole of the left coronary arterial bed (Fig. 1c). There were two areas of severe stenosis on the left anterior descending and circumflex arteries which explain the limited progression of the guide-wire. During this injection, ventricular fibrillation occurred, whereas the electrocardiogram had shown only occasional broad complexes since the onset of the resuscitative measures. After three cardioversions, sinus rhythm reappeared and blood pressure immediately returned to initial values. A few minutes later, spontaneous breathing resumed and the patient regained consciousness. Twenty minutes after recanalisation, while lignocaine (2 mg/min) was perfused, another injection of contrast medium confirmed the patency of the left coronary arterial tree.

Her electrocardiogram having returned to normal, the patient was transferred to the intensive care unit where heparin treatment was continued, lignocaine being stopped after a few hours. Enzymatic assays showed an increase of CK to 900 IU with an MB fraction of 3·5%, presumably because of the cardiac massage and cardioversions, and possibly cardiac reperfusion and myocardial damage. After 10 days in hospital, without any chest pain or electrical change, the patient was discharged on beta-blockers. Another coronary angiogram was arranged two months later but this was refused by the patient.

CASE 2

A 67-year-old man had mitral regurgitation of long standing and was investigated on 4 June 1980 because of a recent episode of acute pulmonary oedema. Right heart pressure measurements confirmed unsatisfactory haemodynamics with a pulmonary systolic pressure of 60 mmHg, and a mean pulmonary wedge pressure of 28 mmHg. The arterial catheterisation started with a femoral transcutaneous puncture, followed by selective left ventricular angiography (Cook 7 F Pigtail catheter). The left ventricle was moderately dilated and globally hypocontractile, and mitral regurgitation was severe. Right and left coronary arteries were weakly opacified but the first centimetres of the left anterior descending artery were clearly seen. After ventriculography the Cook 7 F catheter was replaced by a left coronary 8 F Bourassa catheter. This catheter was the wrong shape and it was replaced by another of the same type. The tip of this catheter was positioned by the left coronary ostium, but before any contrast medium could be injected the patient complained of severe constricting chest pain and the electrocardiogram showed significant ST segment elevation in the anteroseptal leads. Extreme bradycardia and cardiovascular collapse followed and the blood pressure remained extremely low

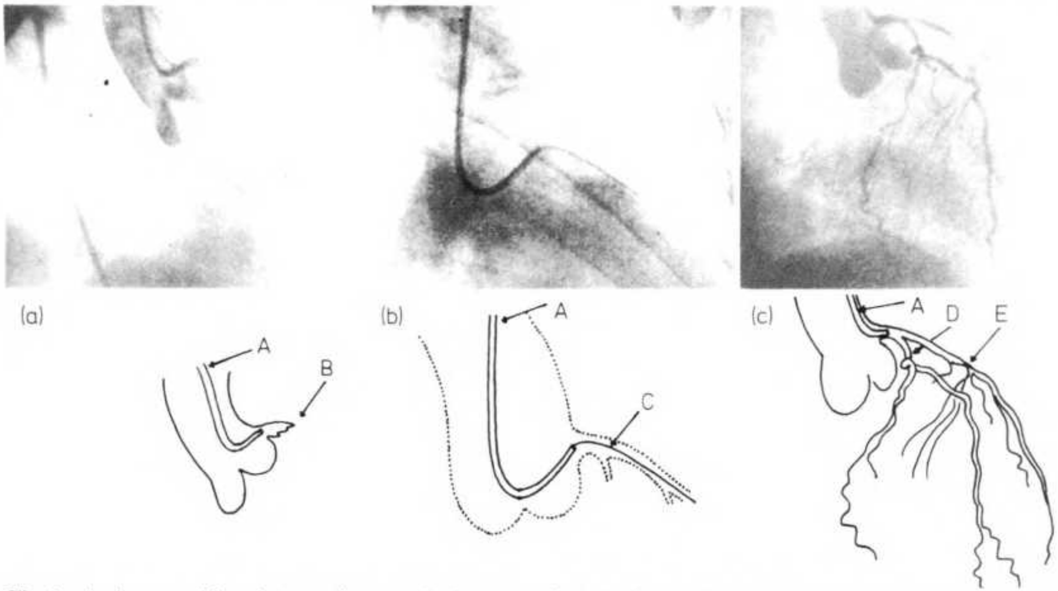

Fig. 1 *Angiograms with explanatory diagrams. A, Coronary catheter in the ascending aorta, with its tip in the left coronary ostium; B, obstructed left main coronary; C, guide-wire pushed into the left anterior descending artery; D, revascularised circumflex artery; E, severe stenosis on the left anterior descending artery.*

despite right ventricular electrical pacing. The alteration of the patient's consciousness and the inefficacy of a dopamine perfusion suggested that his condition was irreversible.

It was decided to obtain an angiogram of the left coronary artery despite the fact that the heart appeared immobile on fluoroscopy. The catheter was changed and yet another Bourassa left coronary catheter was introduced. Opacification showed an obstruction of the anterior descending artery close to its origin from a normal left main coronary (Fig. 2a). The circumflex artery was normal except for severe stenosis at the origin of its obtuse marginal branch.

The intracoronary injection of glyceryl trinitrate, 3 mg, had no effect. A Cordis J guide (diameter 0·35 mm) was then introduced into the left main coronary artery and easily pushed for 6 or 7 cm into the left anterior descending artery (Fig. 2b). Ventricular fibrillation occurred when the guide-wire was removed; the electrocardiogram had previously shown only considerably widened electrostimulated complexes.

Cardioversion promptly restored sinus rhythm, at which time left ventricular contractility reappeared and the systolic blood pressure rose to 120 mmHg.

Another angiogram of the left coronary confirmed the recanalisation of the left anterior descending artery and of its branches. The opacification of this recanalised vascular tree, however, appeared distinctly later than that of the circumflex, suggesting that the disobliteration had been incomplete. The catheter tip was advanced to the origin of the left anterior descending artery and streptokinase, 20 000 units, was slowly injected through the catheter for two minutes. Just after this, another angiogram showed symmetrical flow in both left coronary branches, confirming improvement in the quality of the recanalisation (Fig. 2c). After these procedures the patient's clinical state was satisfactory, without chest pain, and with a stable blood pressure. Electrocardiograms showed persistence of ST segment elevation in leads I and aVL. He was transferred to the intensive care unit where lignocaine, 2 mg/min, was given for 24 hours, in addition to heparin and digitalis and diuretic treatment. CK rose to 660 IU, with a 7% MB fraction, the increase in enzyme levels presumably being the result of a high lateral necrosis which was confirmed by the subsequent appearance of a Q wave in lead I and aVL. After good clinical progress the patient was discharged two weeks later. At a second investigation before mitral valve replacement, two months after this, the patency of the left coronary tree was confirmed. There was a severe stenosis at the origin of the anterior branch of the circumflex, and another less

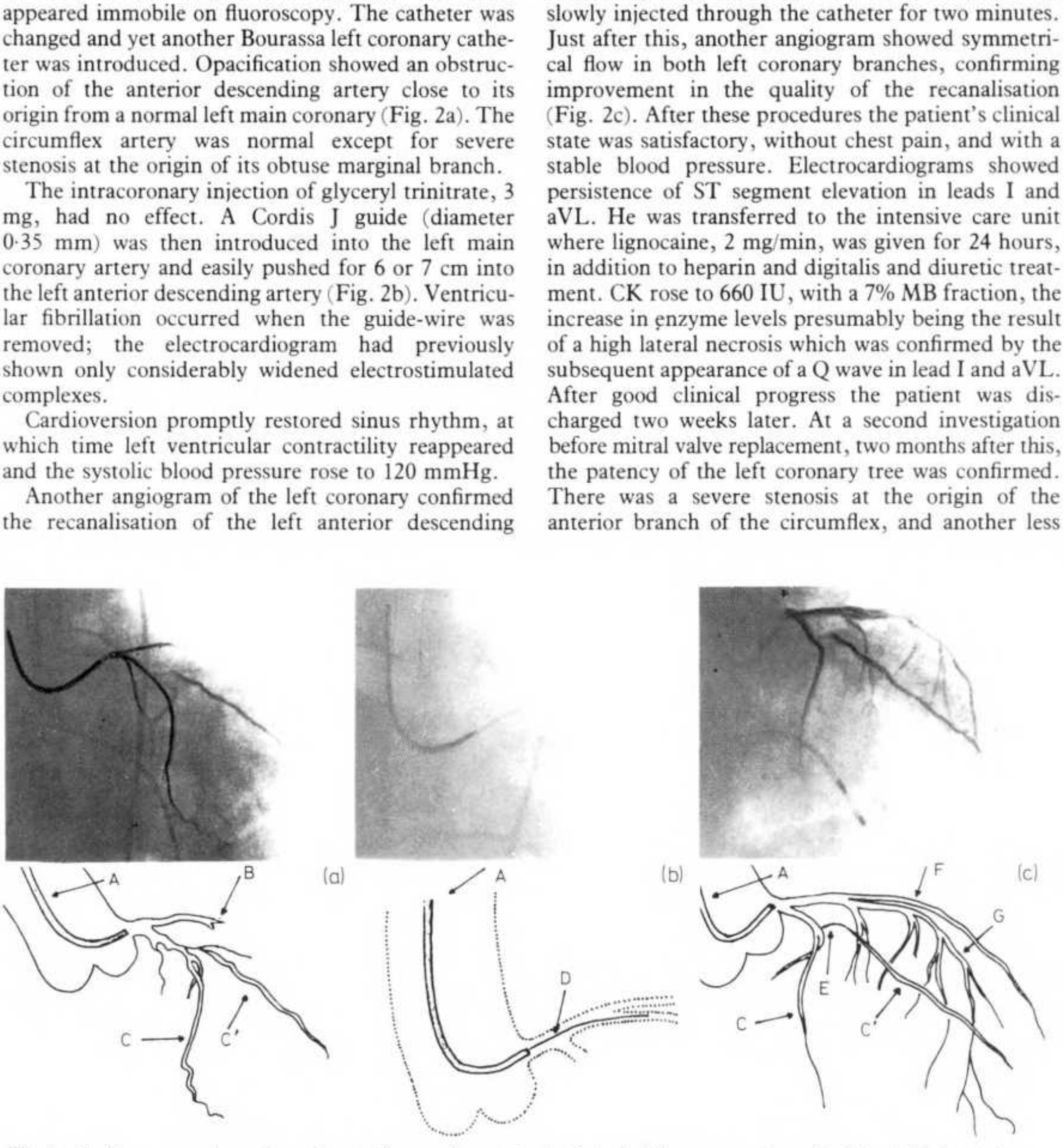

Fig. 2 *A, Coronary angiography catheter in the ascending aorta, its tip in the left coronary ostium; B, obstructed left anterior descending artery; C, circumflex artery; C', obtuse marginal branch; D, guide-wire pushed into the left anterior descending artery; E, severe stenosis at the origin of obtuse marginal branch; F, revascularised diagonal branch; G, revascularised left anterior descending artery.*

The right ventricular pacing catheter and the part of the catheter in the ascending aorta which are visible on the photographs are not shown on the diagrams.

severe stenosis at the origin of the left anterior descending artery.

Successful valvular replacement and aorto-circumflex bypass grafting followed.

Discussion

Coronary angiography, though routinely performed, is not totally devoid of danger. Published reports indicate a number of complications and death is not exceptional, occurring in approximately 0·4% of cases, the figure varying considerably.[4-11] These variations seem to depend at least in part on the experience of the operators and the techniques used but also on whether or not deaths occurring up to 48 hours[8] or even 10 days later[11] are included.

Acute myocardial ischaemia leading to death from cardiogenic shock and electromechanical dissociation is a serious complication in coronary angiography, death often occurring during the examination itself.[5] Probably in most cases this is caused by acute coronary occlusion, the angiographic criterion of which is the sudden obstruction of a previously opacified patent coronary artery. In some cases this can result from a traumatic intimal dissection,[5 12] from persistent spasm,[7] or, classically, from the mobilisation of an atheromatous plaque, but in most cases it is the result of thrombus originating from the catheter. In an angiographic and anatomical study of 66 deaths occurring during coronary angiography, Takaro *et al.*[11] found this to be the case in 35 patients, that is 53% of their cases. In most series however, this cause, though strongly suspected, is not proven.[4 10 13] Bourassa and Noble[5] found a fresh intracoronary thrombus only twice and histological evidence for recent infarction only three times in nine necropsies on patients who had developed sudden ischaemia during coronary angiography.

In our two cases, the diagnosis of intracoronary thrombosis was strongly suspected on angiography by the appearance of abrupt termination of the left coronary artery. In both, the total absence of effect of intracoronary glyceryl trinitrate probably excluded spasm. The possibility of coronary dissection may be entertained in the first case despite the lack of any typical angiographic evidence, but is not plausible in the second, since the obstruction was several centimetres away from the injection site.

The increased thromboembolic risk of arterial catheterisation by the femoral compared with the brachial route is well documented[4 9-11 14] and could be the result of the use of guide-wires. When the guide is withdrawn from the catheter, the thin layer of platelet aggregates rapidly formed upon it[15] can adhere externally to the catheter tip and then become detached and embolise. This may pass into a coronary ostium, thus causing a coronary obstruction, more often at the site of a proximal severe stenosis.[5 11] Prophylactic intravenous heparin is recommended[10 13 16] but does not eliminate all thromboembolic events, as shown by Bourassa and Noble[5] and as our two cases confirm, since our patients all receive an intravenous dose of 50 mg heparin at the beginning of the procedure.

Though it has sometimes been attempted,[5 10 11 17] emergency aortocoronary bypass is almost always doomed to failure in such instances. In our two cases the simple act of pushing a guide-wire through the obstruction, with or without the intracoronary injection or infusion of fibrinolytic drugs, appeared to be the only possible course of action. We had already had experience with this technique in more than 30 cases of acute myocardial infarction, using the method proposed by Rentrop *et al.*[1] The efficacy of this action in both cases was plain. In the first patient, the guide-wire produced perfect angiographic recanalisation of the left coronary artery and a subsequent injection of streptokinase was not necessary. The immediate result excluded the hypothesis of spontaneous lysis of the clot. In the second patient, the guide passed through the obstruction but a noticeable delay in the opacification of the distal coronary bed persisted and an injection of streptokinase improved distal perfusion.

The clinical improvement of both patients after disobliteration was rapid and spectacular. In both, the removal of the guide-wire was followed by ventricular fibrillation which can be interpreted as the consequence of myocardial revascularisation. No electrocardiographic sequelae of the accident occurred in the first case; in the second the subsequent high lateral infarction was possibly the result of the obstruction of the stenosed circumflex branch not reached by either the guide-wire or the streptokinase.

Thus, the occurrence of sudden myocardial ischaemia during coronary angiography may be caused by accidental coronary occlusion. However critical the clinical state may be, it is essential to define the site and type of the obstructive lesion by a selective injection of contrast medium while resuscitative measures are continued. If thromboembolism is suspected, it is legitimate to try transluminal recanalisation. The technique is simple and can produce a dramatic reversal of an apparently hopeless situation.

The authors wish to thank Mr N Moore for his assistance in the translation of this manuscript.

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Br Heart J 1982; 47: 249–52

Two cases with spontaneous spasm of left main trunk

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SUMMARY Two cases with spontaneous spasm of the left main trunk are described. Collateral vessels were visualised during spasm in both cases, and disappeared after its relief by the administration of nitrites.

Coronary artery spasm may cause the various types of angina pectoris,[1–3] and if it occurs spontaneously during coronary arteriography it may be mistaken for an organic stenosis.[4–10] The distinction between spasm and fixed obstruction is important, especially when it is located in a critical site. We describe two cases with spontaneous spasm of the left main trunk associated with visualisation of collateral vessels which might easily have been confused with arteriosclerotic stenosis.

Case reports

CASE 1

A 36-year-old housewife was admitted to hospital with a two month history of an oppressive sensation in the precordium on exertion and at rest. Physical examination was normal.

The resting electrocardiogram showed inverted T waves in leads V1 to V4. ST segment depression in leads V2 to V6 occurred during precordial oppression at rest and just after double Master's test.

Cardiac catheterisation was performed using Sones's technique. When the catheter was advanced into the innominate artery, the patient complained of an oppressive sensation in the precordium and there was ST segment depression in leads V2 to V6. Coronary angiography at that time disclosed 90% narrowing of the left main trunk (Fig. 1a) and collateral vessels (Fig. 1b) to the left anterior descending artery from the right coronary artery through the interventricular septum. Angiography was repeated after spontaneous resolution of the symptoms and ST changes. Narrowing of the left main trunk had become less, and the collateral vessels were hardly seen.

Subsequently she exercised on a bicycle ergometer, pedalling at a workload of 35 W. After one minute of exercise the precordial discomfort and ST segment depression recurred. Coronary angiograms were obtained immediately and showed the same abnormalities as those occurring during the spontaneous attack. After sublingual administration of 0·6 mg glyceryl trinitrate and injection of 10 mg isosorbide dinitrate into the sinus of Valsalva, only 25% stenosis of the left main trunk (Fig. 1c) was present. The left anterior descending, left circumflex, and right coronary arteries were normal, and collateral vessels were no longer visible (Fig. 1d).

CASE 2

A 53-year-old man presented to hospital with anterior chest pain at rest during the day and on walking, especially in the early morning. This pain, relieved by sublingual adminstration of glyceryl trinitrate, appeared two and half months before admission. Physical and laboratory examinations showed nothing abnormal. The resting electrocardiogram was normal. The double Master's test performed in the early morning was positive with ST segment depression in leads V4 and V5, and the same test in the afternoon was negative.

Coronary arteriography by Sones's technique was carried out. Chest pain occurred spontaneously, with ST segment depression from leads V3 to V6 just before the catheter was introduced into the brachial artery. Coronary angiograms, which were obtained immediately, disclosed extreme narrowing of the left main trunk and delayed filling of the left anterior descending artery without visualisation of the circumflex artery (Fig. 2a). Collateral vessels to both the left anterior descending and circumflex arteries from the right coronary artery were seen (Fig. 2b).

Narrowing of the left main trunk became less severe and collateral vessels disappeared when the chest pain was relieved by sublingual administration of 0·3 mg glyceryl trinitrate. Then 0·1 mg ergonovine maleate was administered into the sinus of Valsalva. Two minutes later chest pain recurred. Both the electrocardiogram and coronary angiograms showed simi-

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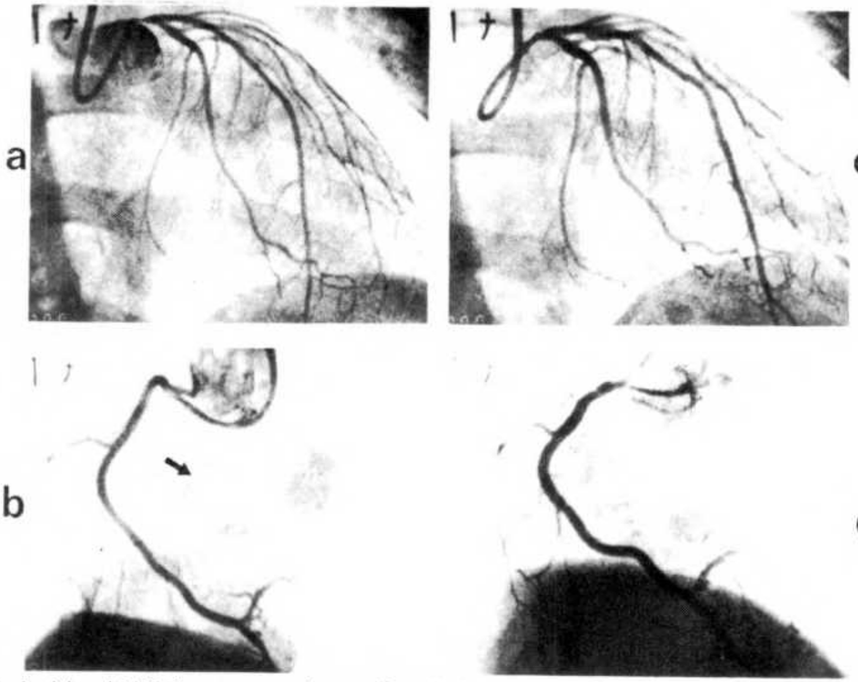

Fig. 1 *(a) and (c) Left coronary arteriogram. (b) and (d) Right coronary arteriogram. (a) and (b) Obtained during spontaneous anginal attack. The arrow (b) indicates collateral vessels to the left anterior descending artery from the right coronary artery through the interventricular septum. (c) and (d) Obtained after administration of nitrites.*

lar findings to those seen during the spontaneous attack of pain.

The left main trunk had minimal irregularity on the arteriograms obtained after an additional 0·6 mg glyceryl trinitrate sublingually and 10 mg isosorbide dinitrate into the sinus of Valsalva (Fig. 2c). The left anterior descending, circumflex (Fig. 2c), and right coronary artery (Fig. 2d) were free from obstruction. The collateral vessels were not seen (Fig. 2d).

Discussion

Coronary spasm plays an important role in the genesis both of the variant form of angina pectoris and angina occurring at rest with ST segment depression.[1] It may be provoked by exercise accompanied by ST segment elevation[2] or depression,[3] and it frequently develops spontaneously during coronary arteriography.[4,5] The occurrence of spasm of the left main trunk, however, is relatively uncommon.[5–7] It has been ascribed to mechanical irritation of the catheter,[8,9] but the spasm seen in our cases cannot have been induced in this way because chest symptoms occurred with ST segment depression before the catheter was introduced into the lumen of the left coronary artery. Furthermore, similar spasm was evoked by leg exercise in case 1 and administration of ergonovine maleate in case 2; it has been shown that there are similarities between spontaneous spasm and spasm provoked by ergonovine maleate.[11–13]

Collateral vessels were seen transiently during spasm in our cases. Collateral channels are thought to exist anyway,[14,15] though under normal conditions they are not functional. It is likely that the perfusion pressure gradient between the right and left coronary artery produced by spasm of the left main trunk brought such channels into play.[16] This phenomenon was not observed in previous studies.[5–10]

Narrowing of the left main trunk should be carefully assessed because it has serious clinical implications.[17,18] Murphy *et al.*[9] emphasised that spasm should particularly be suspected in cases of isolated obstruction of the trunk because atherosclerotic obstruction is usually associated with multiple vessel involvement.[17,18] Angiographic demonstration of collateral vessels does not confirm that a stenosis is organic. Sufficient nitrites must be given to relieve spasm lest it should be mistaken for fixed obstruction.

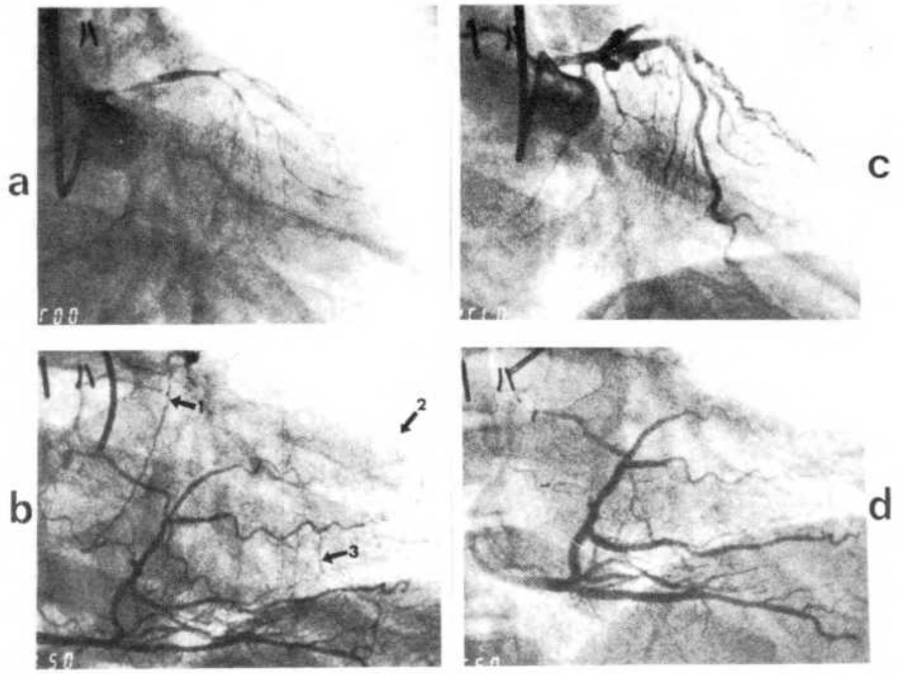

Fig. 2 *(a) and (c) Left coronary arteriogram. (b) and (d) Right coronary arteriogram. (a) and (b) Obtained during spontaneous chest pain attack. The arrows 1, 2, and 3 indicate the collateral vessel from the right coronary artery to the left circumflex artery, the diagonal branch, and the left anterior descending artery, respectively. (c) and (d) Obtained after administration of nitrites.*

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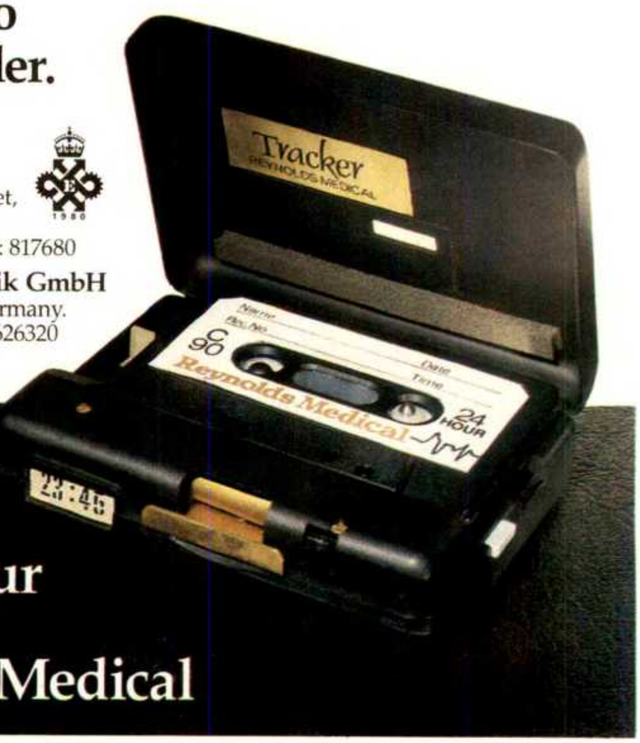

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Non-invasive assessment of changes in left ventricular relaxation by combined phono-, echo-, and mechanocardiography

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SUMMARY In order to investigate interrelations between early diastolic events, simultaneous apex-, phono-, and echocardiograms were recorded in 10 normal subjects and 55 patients with ischaemic heart disease. In normal subjects isovolumic relaxation time measured as A2 to mitral valve opening was 72±9 ms, the interval A2−0 point was 116±15 ms, and the amplitude of the f wave of the apexcardiogram relative to the total amplitude was 11±2%. In patients with a normal left ventricular end-diastolic pressure (<15 mmHg), isovolumic relaxation time was prolonged to 99±18 ms, A2−0 point to 162±5 ms, and the relative height of the f wave was increased to 21±4%. Isovolumic relaxation time and A2−0 point interval both showed significant inverse correlation with left ventricular diastolic pressure. Glyceryl trinitrate administration or isometric stress both caused well recognised changes in arterial pressure and cavity size. Neither had any additional effect during early diastole in normal subjects. In the patients, however, glyceryl trinitrate prolonged isovolumic relaxation time, delayed the 0 point of the apexcardiogram with respect to A2, increased the interval 0 point − f wave, and reduced the relative amplitude of the f wave. Isometric stress had the opposite effects. These changes extend beyond the end of ventricular relaxation and so are more readily explained on a mechanical basis, possibly as oscillations whose periodicity and degree of damping were increased by glyceryl trinitrate and decreased by isometric stress.

Disturbances of relaxation form an important component of left ventricular disease, so that their non-invasive investigation may have appreciable clinical significance. In addition, it is clear that diastolic events can be influenced pharmacologically in a way that cannot be predicted from observations in normal subjects.[1] In the present study, therefore, we examined the haemodynamic and other determinants of a series of well-defined diastolic time intervals in normal subjects and patients with ischaemic heart disease. It was our purpose to investigate mechanisms underlying resting abnormalities in these patients, and to assess the extent and nature of their alteration with glyceryl trinitrate administration or isometric stress.

Subjects and methods

We investigated 10 normal subjects and 55 patients with ischaemic heart disease, 16 of whom were on therapeutic doses of beta-blocking drugs at the time of study. All patients had the diagnosis confirmed by cardiac catheterisation and coronary arteriography; in 30, the investigation was performed within 48 hours of cardiac catheterisation and in those patients, diastolic time intervals were correlated with haemodynamic values.

Non-invasive measurements were made with the patients supine and in the left semilateral position. Simultaneous echo-, phono-, and apexcardiograms were recorded along with standard lead II of the electrocardiogram using Cambridge Instruments equipment. Echocardiograms were recorded at the level of the tips of the mitral valve leaflets, to show the time of separation of anterior and posterior cusps at the start of ventricular filling. Left ventricular cavity size was estimated at this level as the distance between the leading edges of the echoes from the left side of the septum and the endocardium of the posterior wall. Phonocardiograms were recorded from the left sternal edge, using a medium or high frequency filter, in the

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position where A2, the onset of the initial high frequency vibration of the aortic component of the second sound, was most obvious. This was definitively identified either from its relation to the dicrotic notch of the indirect carotid pulse, or from the aortic valve echogram (Fig. 1). Apexcardiograms were recorded using a transducer of time constant 4 seconds and lower frequency limit of 0·05 Hz. Records were made photographically at a paper speed of 100 mm/s, and digitised.[2]

MEASUREMENTS

From these records, the following measurements were made:

(1) *Time intervals*

(a) Isovolumic relaxation, as the interval between A2 and the onset of mitral valve opening (Fig. 1). Measurements of this time interval were made blindly by two independent observers. In each patient results from five successive beats were meaned.

(b) A2 to the 0 point of the apexcardiogram.

(c) 0 point to the peak of the f wave of the apexcardiogram (Fig. 2).

(2) *Relative amplitude of f wave of apexcardiogram, expressed as a percentage of total amplitude* (Fig. 2)

(3) *From digitised echocardiograms*

(a) End-diastolic (synchronous with the q wave of the electrocardiogram) and minimum cavity dimension.

(b) Peak normalised rate of change of dimension during systole (peak VCF).

(c) Any dimension change during isovolumic relaxation.

(d) The time interval between A2 and minimum dimension.

(e) Delay in mitral valve opening, with respect to minimum dimension.

Contraction pattern was described as synchronous when A2 preceded minimum cavity dimension by more than 20 ms, and asynchronous when A2 preceded by less than 20 ms, or was synchronous with minimum dimension.[1]

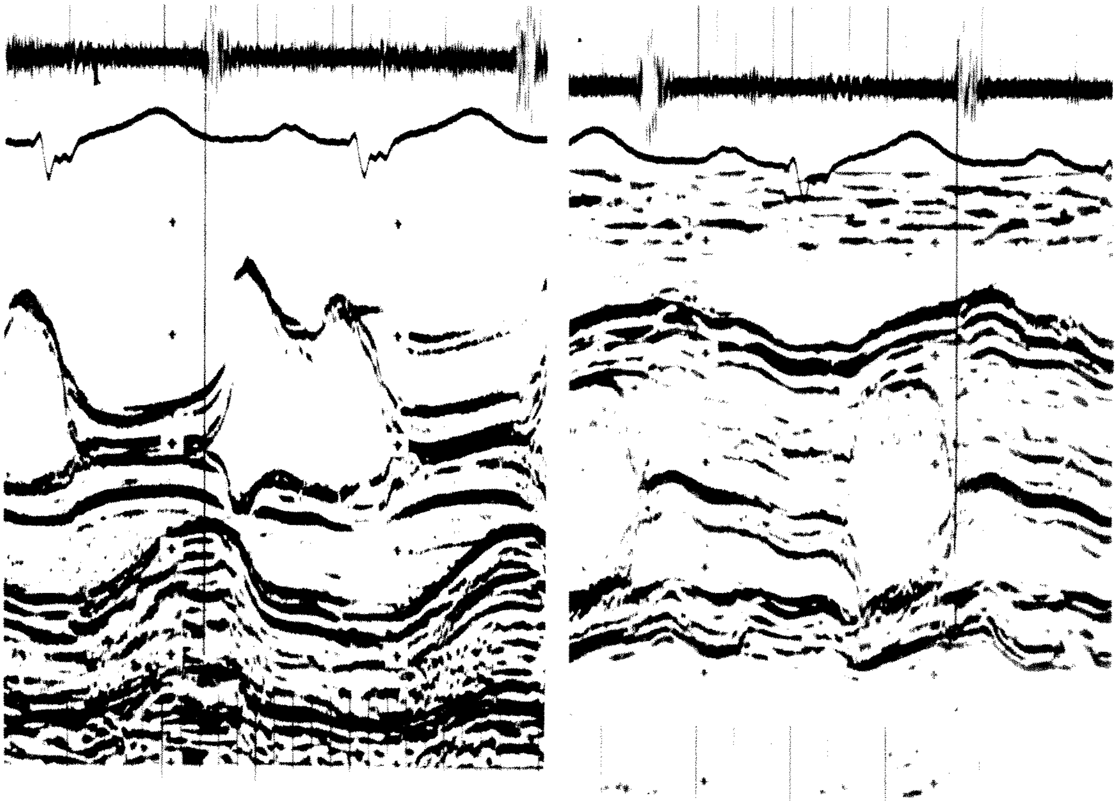

Fig. 1 *Measurement of isovolumic relaxation time as the time interval from A2 to mitral valve opening (left panel). The timing of the onset of the first high frequency component of A2 as aortic valve closure is confirmed from the aortic echogram on the right.*

Thirty patients performed isometric stress when they had completed control measurements. The patients squeezed a sphygmomanometer bulb at 30% of the maximum force that they could generate for a period of three to five minutes, until the onset of fatigue. Recordings were made during the last 30 seconds of effort. No patient developed anginal pain or significant ST segment changes during this time. After 20 minutes' rest, control measurements were repeated, and the patients took two 0·5 mg glyceryl trinitrate tablets sublingually over an interval of five minutes. Measurements were repeated at two, five, ten, and 20 minutes, and those coinciding with the maximum heart rate response were noted.

The statistical significance of differences between mean values was assessed by Student's t test. Linear regression analysis was by the method of least squares. Fourfold tables were analysed by Fisher's exact probability test.

Results

(1) ISOVOLUMIC RELAXATION TIME

Normal isovolumic relaxation time was 72±9 ms (mean ±1 standard deviation). In patients with ischaemic heart disease, the mean value was 68±37 ms, not significantly different. (The mean values for isovolumic relaxation time in normals and patients with ischaemic heart disease for the two observers were 73±9 compared with 70±10 and 66±43 compared with 69±47, respectively. The correlation coefficient for the plot of one observer's values against the other observer's values was 0·91).

Isovolumic relaxation time was unrelated to peak, diastolic, or mean aortic pressure. There was, however, significant correlation with left ventricular end-diastolic pressure (Fig. 3), given by the equation:

$$IVR=126-4{\cdot}0 \text{ (pre "a" LVEDP)},$$

$R=-0{\cdot}87=20$ ms, where IVR is isovolumic relaxation time and LVEDP is left ventricular end-diastolic pressure. Standard error of the estimate=20 ms.

In patients with a high left ventricular end-diastolic pressure, therefore, the duration of the isovolumic relaxation time was reduced, in some cases to 0 ms (Fig. 1). In patients with left ventricular end-diastolic pressure less than 15 mmHg considered in isolation, isovolumic relaxation time was prolonged to 99±18 ms, significantly longer than in the normal group ($p<0{\cdot}01$). There was no relation between contraction pattern, whether synchronous or asynchronous, and isovolumic relaxation time.

(2) A2–0 POINT INTERVAL

This interval was 116±15 ms in normal subjects,

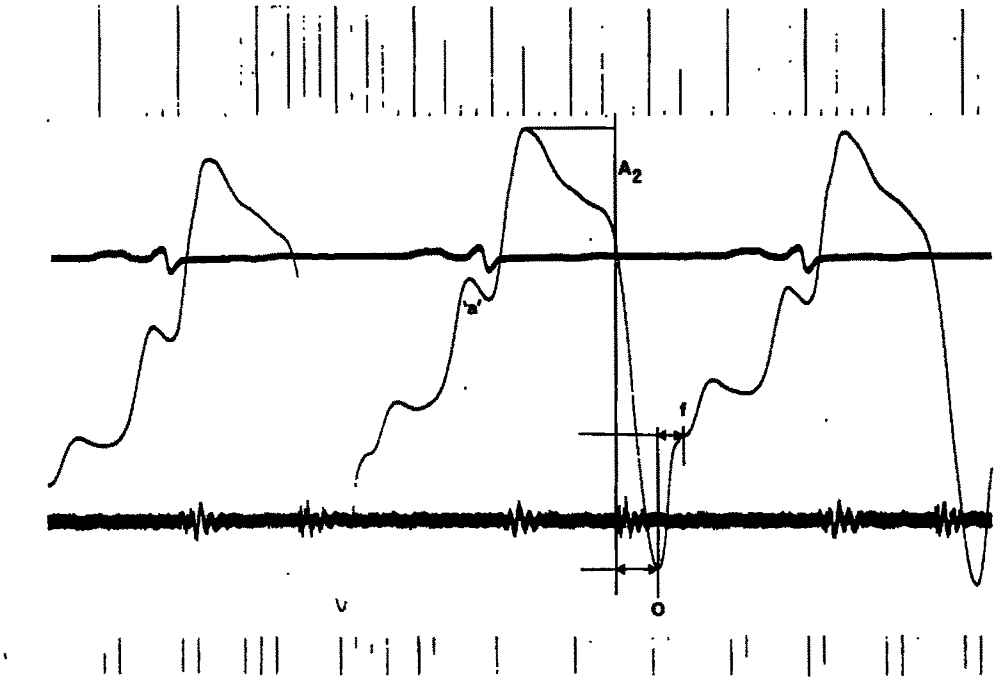

Fig. 2 *Representative apexcardiogram, showing measurements of the intervals A2–0 point, 0–f, and relative amplitude of the f wave.*

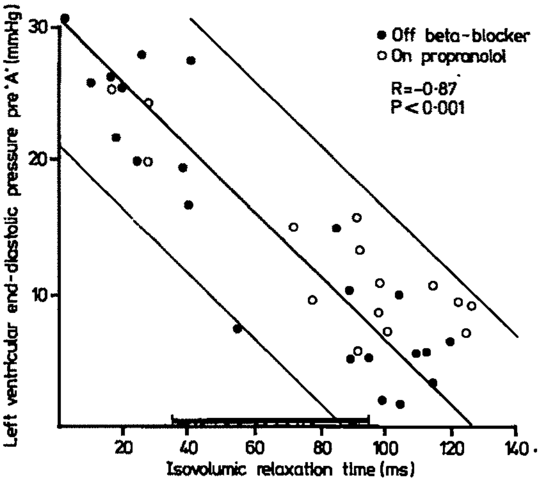

Fig. 3 *Relation between isovolumic relaxation time and left ventricular end-diastolic pressure in patients with ischaemic heart disease. The 95% confidence limits normal for isovolumic relaxation are indicated by the horizontal bar.*

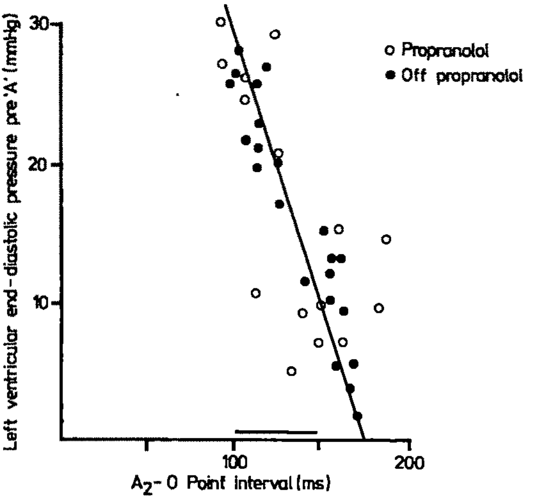

Fig. 4 *Relation between left ventricular end-diastolic pressure and the interval A2−0 point in patients on or off beta-blocking drugs. The 95% confidence limits normal for A2−0 point interval are indicated by the horizontal bar.*

significantly longer than isovolumic relaxation time, since the 0 point consistently follows mitral valve opening. Again, in the whole group of patients with ischaemic heart disease, it was not significantly prolonged, being 130±24 ms. There was, however, strong inverse correlation with end-diastolic pressure, given by the regression equation:

$$A2-0=175-2{\cdot}5\ (\text{pre "a" LVEDP})$$
$$R=-0{\cdot}95,\ \text{SEE } 23\ \text{ms}$$

for patients not on beta-blockers. For those on beta-blockers the correlation was significantly less good (Fig. 4).

The resulting relation between end-diastolic pressure and the interval mitral valve opening (MVO) to 0 point is given by the regression equation:

$$MVO-0=44+1{\cdot}76\ (\text{pre "a" LVEDP}),\ R=0{\cdot}77,$$
$$\text{SEE}=13\ \text{ms.}$$

The interval A2−0 point in patients with ischaemic heart disease and normal left ventricular end-diastolic pressure was significantly prolonged to 162±5 ms ($p<0{\cdot}01$), with respect to normal.

(3) AMPLITUDE AND TIMING OF F WAVE

In normal subjects the peak of the f wave occurred 75±10 ms after the 0 point, and its relative amplitude was 11±2%. In patients with raised end-diastolic pressure, the relative height of the f wave was significantly increased to 21±4%. There was also a non-linear relation between the duration of isovolumic relaxation and the relative amplitude of the f wave (Fig. 5), so that as isovolumic relaxation time fell below 40 ms, the height of the f wave increased strikingly.

EFFECTS OF GLYCERYL TRINITRATE AND ISOMETRIC EXERCISE

(1) *Heart rate, arterial pressure, and cavity dimensions*

These are given in detail in Fig. 6. Glyceryl trinitrate caused a significant increase in heart rate and a reduction in systolic and diastolic blood pressure. Cavity dimensions also fell at end-systole and end-diastole. Isometric stress caused increases in heart rate, and in systolic and diastolic blood pressures. In contrast to glyceryl trinitrate, cavity dimensions increased at end-diastole and end-systole. There were no significant differences in the behaviour of any of these variables between the normal subjects and those with coronary artery disease, whether contraction pattern was co-ordinate or incoordinate.

(2) *Diastolic time intervals*

In patients with ischaemic heart disease, glyceryl trinitrate caused significant prolongation of isovolumic relaxation by 23 ms, which was highly significant ($p<0{\cdot}01$). Prolongation of isovolumic relaxation time was greatest in patients with high filling pressures but also occurred in patients with normal filling pressures.

A2 to the 0 point was also prolonged by 12 ms ($p<0{\cdot}01$). This was less than the delay in mitral valve opening, so that the interval mitral valve opening to the 0 point was significantly shortened. At the same time, the 0–f interval was prolonged by 20 ms

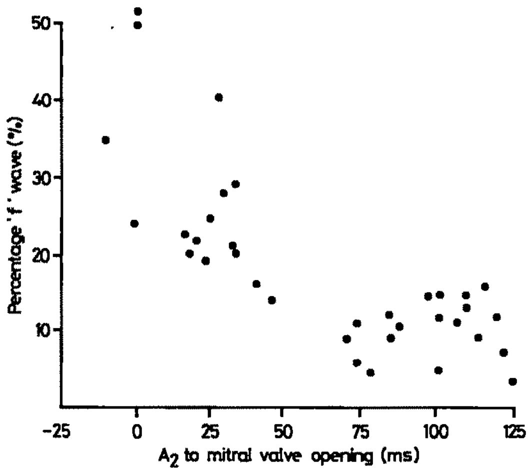

Fig. 5 *Relation between isovolumic relaxation time and the relative height of the f wave (%f).*

($p<0.01$), and the relative amplitude of the f wave fell by 23% of the initial value.

Isometric stress caused isovolumic relaxation time to shorten by 17 ms ($p<0.01$) in the patients. A2–0 point and 0–f intervals also tended to shorten, though the sample size was small for these measurements, because of technical difficulties in obtaining apexcardiograms during exercise. There were no changes in A2 – MVO or A2 – 0 point intervals in normal subjects in response to glyceryl trinitrate or isometric handgrip.

(3) *Relation of changes in diastolic time intervals to resting contraction pattern*

Changes in diastolic time intervals correlated with resting contraction pattern. In 15 patients with ischaemic heart disease and a normal left ventricular end-diastolic pressure, nine responded to glyceryl trinitrate administration with changes in isovolumic relaxation time; of these, seven had a synchronous contraction pattern and two an asynchronous pattern. All of the six patients who failed to respond to glyceryl trinitrate had an asynchronous contraction pattern ($p<0.01$). Of 11 patients who underwent isometric stress testing, seven had shortening of isovolumic relaxation time, and in six of these contraction was synchronous. Of the four patients not responding to isometric handgrip, all four were asynchronous ($p<0.02$).

(4) *Contraction and relaxation pattern*

Glyceryl trinitrate did not affect peak shortening, but there was a significant increase in dimension change during the time of inscription of the downstroke of the apexcardiogram ($p<0.05$) from 37±20% to 48±30%, while mitral valve opening was further delayed with respect to minimum dimension ($p<0.05$) by 23±4 ms. Isometric stress caused peak shortening to fall significantly ($p<0.05$). It did not alter left ventricular dimensions during either the upstroke or the downstroke of the apexcardiogram but led to a reduction in the delay of mitral valve opening with respect to minimum dimension by 30±5 ms ($p<0.01$).

(5) *Effect of beta-blocking drugs*

Of the 55 patients in this study, 16 were on long term beta-blockade. There was no correlation between treatment and resting contraction pattern (whether co-ordinate or incoordinate), or between end-diastolic pressure and diastolic time intervals except that patients on beta-blockers showed a poorer correlation between left ventricular end-diastolic pressure and A2–0 point interval. No aspect of the response to glyceryl trinitrate or isometric stress was significantly altered in patients taking beta-blocking drugs.

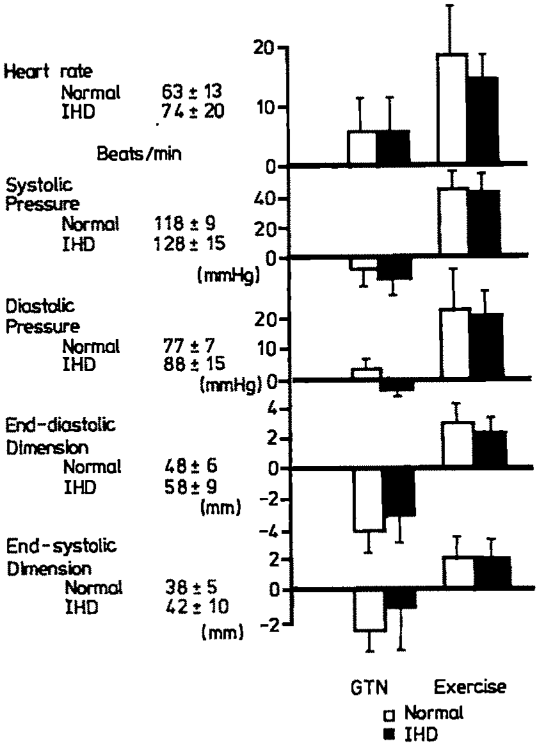

Fig. 6 *Changes in heart rate, systolic and diastolic blood pressure, and end-systolic and diastolic dimension with glyceryl trinitrate (GTN) and isometric stress.*

Discussion

Non-invasive methods can be used to define a series of events during early diastole, including A2 from the phonocardiogram, and the 0 and f points of the apexcardiogram. None of these coincides precisely with measurements obtained invasively. Thus A2 bears no fixed relation to the timing of peak negative dP/dt, mitral valve opening may precede the cross-over of atrial and ventricular pressures,[3] the 0 point of the apexcardiogram, though close to the nadir of the pressure pulse, is not synchronous with it,[4] and the f wave, corresponding to the third heart sound, has no invasive counterpart. These non-invasive measurements are reproducible, however, and represent a series of events of considerable physiological or pathological significance, so that their study becomes a legitimate object of inquiry in its own right.

Mean values for isovolumic relaxation time reported here agree with those previously reported.[5] The increased scatter of values about the mean, seen in patients with ischaemic heart disease, was unrelated to aortic pressures, but could be largely explained on the basis of left ventricular end-diastolic pressure, to which isovolumic relaxation time was strongly and negatively correlated. In the group of patients in whom end-diastolic pressure was normal, isovolumic relaxation was very significantly prolonged to nearly 100 ms, a value almost identical to that previously reported in patients with left ventricular hypertrophy.[5] The mechanism underlying this prolongation was not clear. It was not the result of concomitant left ventricular hypertrophy, nor could it be related to incoordinate wall motion, either during isovolumic contraction or isovolumic relaxation. Prolongation of isovolumic relaxation time thus appears to reflect some other aspect to left ventricular involvement in ischaemic heart disease, which we are, at present, unable to identify.

A raised end-diastolic pressure affected other diastolic events. It was associated with an increase in the prematurity of mitral valve opening with respect to the 0 point, and a decrease in the time interval from A2 to the 0 point. This latter interval has been studied in the past as isovolumic relaxation,[6] but can more usefully be regarded as a measure of the time taken by the left ventricular pressure to fall to its minimum value at the end of ejection. Like isovolumic relaxation, it was longer than normal in patients with ischaemic heart disease, and was also strongly and inversely correlated with end-diastolic pressure. The timing and relative amplitude of the f wave were also related both to the duration of isovolumic relaxation time and to end-diastolic pressure, a high end-diastolic pressure being associated with an earlier f wave of increased relative amplitude. No such relation could be shown between these values and either shortening fraction or peak shortening, which reflect other aspects of left ventricular function. It is apparent, therefore, that these diastolic time intervals do not vary randomly, but that characteristic patterns are seen in patients with ischaemic heart disease, dependent on end-diastolic pressure.

In order to investigate the apparent stability of these patterns further, we attempted to perturb left ventricular function by subjecting it to the effects of glyceryl trinitrate administration or isometric stress. Both interventions caused changes in arterial pressure and cavity size that have previously been described.[7] Neither intervention had any additional effect during early diastole in the normal subjects. In patients with ischaemic heart disease, however, well defined changes were observed. Glyceryl trinitrate prolonged isovolumic relaxation time if it was initially short, delayed the 0 point of the apexcardiogram with respect to A2, increased the interval between the 0 point and the f wave, and reduced its relative amplitude. Conversely, isometric stress shortened isovolumic relaxation and the intervals A2−0 point and 0 point−f wave. Thus, the interrelations between diastolic events were maintained, the changes after glyceryl trinitrate being similar to those expected with a reduction in end-diastolic pressure, and those after isometric stress with an increase. Since the study was performed non-invasively, end-diastolic pressure was not measured directly, though similar changes are well documented.[8] It would clearly be of interest to do so, since an alternative possibility is that changes in diastolic time intervals and end-diastolic pressure both reflect some more fundamental modification in left ventricular properties brought about by these interventions.

Simultaneous M-mode echocardiograms of the left ventricular cavity and apex- or phonocardiograms can be used to detect disturbances in contraction pattern. Normally changes in transverse dimension are small during the time of inscription of the upstroke of the apexcardiogram, which approximates to isovolumic contraction, and during isovolumic relaxation. An asynchronous contraction pattern is shown by significant dimension changes during isovolumic contraction or isovolumic relaxation, representing changes in cavity shape at a time in the cardiac cycle when ventricular volume is constant, and by minimum cavity dimension occurring early, so that it comes to coincide with A2. Analysis of the results in individual patients in the present study showed that the effects of both interventions were determined by basal contraction pattern. Only when contraction pattern was synchronous, did isovolumic relaxation time alter with glyceryl trinitrate or handgrip. When it was asynchronous, the extent of abnormal dimension changes occurring during isovolumic relaxation was modified though their duration remained unchanged. The effects of glyceryl trinitrate are thus similar to those previously shown for propranolol,[1 9] both in their nature and in their sensitivity to basal contraction pattern, though they differ because, with the later drug, they occurred when contraction pattern was asynchronous rather than synchronous.

This consistent pattern seems to require explanation. The changes cannot be explained on the basis of heart rate, and are the exact opposite of what would be predicted from alterations in arterial pressure. The reduction in isovolumic relaxation time with increasing end-diastolic pressure is likely to be, in part, a direct effect of the concomitant rise in left atrial pressure, as has previously been noted in mitral stenosis, and more recently in a variety of other types of heart disease.[10] The lack of sensitivity of isovolumic relaxation time to aortic pressure could be explained on the basis of the close time relation between peak negative dP/dt and A2, so that left ventricular pressure is falling more rapidly when the valve closes than when the mitral valve opens. The basis for the changes in the apexcardiogram is less obvious. The changes were not seen in normal subjects, and are independent of the timing of mitral valve opening, so they bear no necessary relation to left atrial pressure. One possibility is that they represent a clinical manifestation of the load dependence of relaxation,[11] the rate of relaxation, and therefore the rate of pressure fall, altering with changes in end-systolic dimension. Against this idea is their failure to occur in normal subjects in spite of virtually indentical dimension changes. In addition, changes were seen in the 0–f interval, as well as in the relative amplitude of the f wave itself. These events occur well beyond the end of relaxation, suggesting that the passive behaviour of the ventricle had also been modified. Of the passive time-related properties of a fluid-containing ventricle with elastic walls, the most relevant to the present observations appear to be simple mechanical oscillations, whose periodicity and degree of damping were increased by glyceryl trinitrate and decreased by isometric stress. The study of such oscillations in the heart is extremely complex, and indeed the problem of predicting the natural frequency of a fluid filled ventricle of irregular shape has not been solved completely. In general terms it is possible to state that the natural frequency is proportional to the mass of the system and the stiffness of the walls, and tends to be greater when the cavity is spherical. There is no evidence that glyceryl trinitrate or propranolol caused an increase in end-systolic cavity size or a change in shape, but their effect on diastolic events might be explained by their altering the passive stiffness of the ventricular walls. It may be significant that such an effect on pressure volume relations has been observed for both drugs later in diastole.[8 12] The presence of such oscillations would have clear implications both for interpreting diastolic events, and for understanding the relation between the time course of relaxation in the myocardium and the cavity pressure trace, so that further investigation of their possible presence seems justified.

These theoretical considerations apart, the observations reported here have clinical significance. They indicate that prolongation of isovolumic relaxation occurs consistently in patients with coronary artery disease, and that it reflects some so far unidentified aspect of left ventricular involvement in this condition. A short isovolumic relaxation time, in the absence of mitral valve disease, is good evidence of a raised end-diastolic pressure. We have used this observation to monitor the long term effects of nitrates in patients with severe left ventricular disease. The occurrence of a group of changes involving several independent variables reduces the uncertainty with which observations can be made, and increases the conviction of abnormalities detected in individual patients. The repreducible nature of these non-invasive measurements adds weight to the contention that they have become useful tools in the study of normal and abnormal diastolic events in man.

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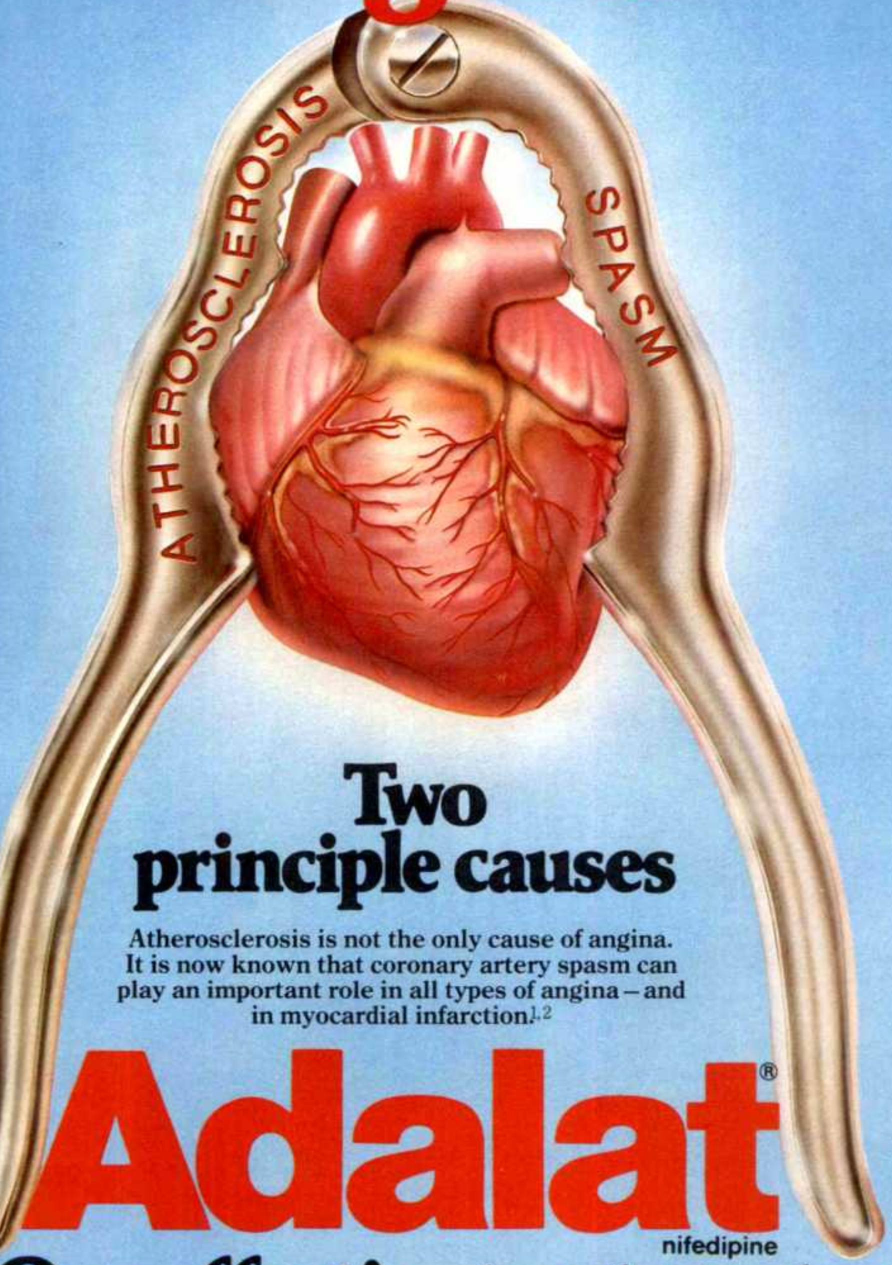
Angina



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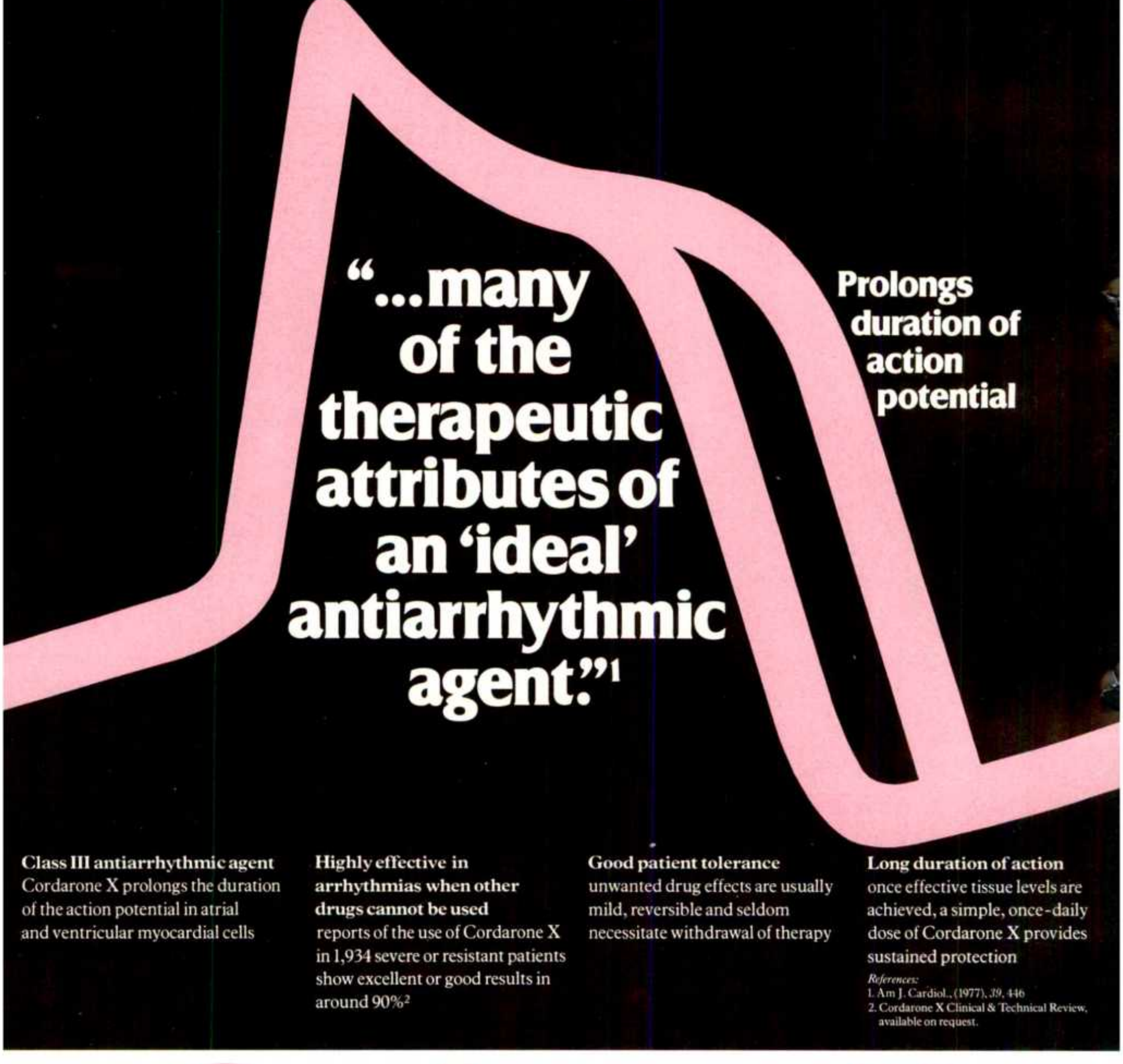
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Br Heart J 1982; 47: 261-9

Postextrasystolic changes in systolic time intervals in the assessment of hypertrophic cardiomyopathy

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SUMMARY To determine if postextrasystolic changes in systolic time intervals can be used to estimate the severity of resting or provocable left ventricular outflow pressure gradient, we studied the cardiac catheterisation records of 42 patients with hypertrophic cardiomyopathy looking for instances of a single premature beat preceded by a control sinus beat and followed by a postpremature sinus beat. There were 75 such instances in 25 patients. In comparison to the control beat, the pre-ejection period in the postpremature beat was shorter by $\Delta PEP = -20 \pm 11$ ms in 73 of 75 instances, and remained unchanged in two. The ejection time in the postpremature beat was invariably longer by $\Delta ET = 37 \pm 20$ ms (range: 10 to 85 ms) and the pre-ejection period/ejection time ratio lower than control by $\Delta(PEP/ET) = -0{\cdot}10 \pm 0{\cdot}05$ (range: $-0{\cdot}01$ to $-0{\cdot}25$). Total electromechanical systole in the postpremature beat was shorter (11/75), the same (10/75), or longer (53/75) than in the control beat, the overall change being $\Delta EMS = 18 \pm 22$ ms. Both ΔPEP and Δ(PEP/ET) correlated poorly with the systolic peak left ventricular-aortic pressure gradient in either the control beat (Gc) or the postpremature beat (Gx), and also with the change in gradient (ΔG) from the control to the postpremature beat. In contrast, significant linear correlations were found between ΔEMS and either Gc, Gx, or ΔG; and also between ΔET and either Gc, Gx, or ΔG. Since internal and external measurements of ejection time are known to be almost identical, the regression equation ($\Delta G = 1{\cdot}65\ \Delta ET - 9$) relating ΔET and ΔG should be useful for the non-invasive assessment of the magnitude of provocable left ventricular outflow pressure gradient in patients with hypertrophic cardiomyopathy with spontaneous or externally-induced premature beats.

Despite a recent surge of interest in the role of rhythm[1 2] and compliance[3 4] disturbances in the morbidity and mortality of hypertrophic cardiomyopathy, information concerning the presence and severity of the systolic left ventricular outflow pressure gradient is still considered useful in both the diagnosis and, possibly, the management of this disease. Such information is readily obtainable by cardiac catheterisation, but the invasive nature of this procedure renders it inconvenient for serial observations on either the evolution of the disease or the effectiveness of specific treatment directed at improving or eliminating the gradient. Consequently, a non-invasive method for estimating left ventricular outflow pressure gradient was sought, and several attempts to use either echocardiography[5 6] or the systolic time intervals[7] to this end have provided encouraging results.

Because of its dynamic nature and pronounced lability, the left ventricular outflow pressure gradient as usually determined at rest can hardly be considered to reflect the actual magnitude of pressure overload borne by the left ventricle under the non-basal conditions of daily activity with the attendant fluctuations of its preload, afterload, and inotropic state. Therefore, the behaviour of the left ventricular outflow pressure gradient under conditions known to aggravate it should be an important consideration in the evaluation and follow-up of patients with this disease.

The purpose of this study is to examine if the effect of postextrasystolic potentiation on the systolic time intervals provides quantitative information on the responsiveness of the left ventricular outflow gradient to positive inotropic stimulation.

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Methods

The records of all patients with hypertrophic cardiomyopathy documented by cardiac catheterisation in our institution since 1970 were retrospectively reviewed for the presence of spontaneous or induced premature beats. These beats could be either ventricular or supraventricular, since the inotropic effect of postextrasystolic potentiation is known to be related to the prematurity rather than to the site of origin of the premature beat.[8] The criteria used for selection were: (1) absence of congenital shunt lesion or valvular heart disease other than mild mitral or aortic regurgitation (regurgitant fraction <20%); (2) absence of major arrhythmias other than occasional ectopic beats; (3) absence of atrioventricular or interventricular conduction abnormalities except for first degree atrioventricular block or right bundle-branch block, because these have no known effect on the systolic time intervals; (4) absence of left ventricular failure as evidenced by angiographic left ventricular ejection fraction exceeding 0·50; this was necessary because of the prolongation in ejection time known to occur with postextrasystolic potentiation in patients with left ventricular failure[9]; (5) simultaneous recording in the resting state, and at 50 to 100 mm/s paper speed, of pressure signals from the left ventricle and the aorta, with adequate definition of the onset of the upstroke and the dicrotic notch on the aortic pressure signal to permit measurement of the ejection time; (6) presence of a single premature beat preceded by a (control) sinus beat and followed by a (postpremature) sinus beat; the control beat should not be preceded by another premature beat; (7) to ensure adequate degree of prematurity and also to avoid examining a postpremature sinus beat which occurred soon after the premature beat, thus being premature itself, a coupling ratio (interval between the premature beat and the preceding sinus beat, divided by control RR interval) of <0·90 and a compensatory pause equal to or longer than the control RR interval, were arbitrarily selected as criteria for acceptance. Whenever several events fulfilling the last two criteria were identified during the same study, all were included. Out of 66 studies on 42 patients initially examined, only 27 studies on 25 patients eventually qualified, each one providing from one to eight (total = 75) eligible events of postextrasystolic potentiation.

Cardiac catheterisation was carried out under premedication with pethidine 50 mg and quinalbarbitone 50 mg both administered intramuscularly, and included simultaneous recording of left ventricular and central aortic pressures obtained by means of a No. 6 or No. 7 NIH catheter introduced into the left ventricle through the right brachial artery, and a polyethylene (PE 160) catheter inserted into the left brachial artery by the Seldinger technique and advanced to the aorta. The diagnosis of hypertrophic cardiomyopathy was made from the left ventricular cineangiogram using standard criteria[10] and was supported in all cases by the existence of a significant (>30 mmHg) resting left ventricular to aortic systolic pressure gradient, or the development of such in response to isoprenaline infusion, Valsalva manoeuvre, or postextrasystolic potentiation after spontaneous or catheter-induced premature beats.[11] Therefore, all patients had either resting or provocable left ventricular outflow pressure gradients, in addition to the angiographic criteria of the disease.

Peak left ventricular to aortic pressure gradient was the difference between the peak values for left ventricular and central aortic pressures. The systolic time intervals were determined from these pressure signals as previously reported.[7] Thus, ejection time was measured from the onset of the rapid upstroke to the nadir of the dicrotic notch on the aortic pressure signal. Whenever the upstroke included an initial slow component followed by a fast component, the point of transition from the slow to the fast component was taken as the onset of ejection. If the transition was gradual, the onset of ejection was taken at the point where a straight line drawn tangentially to the aortic upstroke separated from the latter. The pre-ejection period was measured as the interval from the onset of the QRS complex to the point where the rising left ventricular pressure signal reached the level of end-diastolic aortic pressure. Total electromechanical systole was the numerical sum of pre-ejection period and ejection time. All measurements were made to the nearest 0·5 mm which represented 10 ms for paper speed of 50 mm/s and 5 ms for paper speed of 100 mm/s. Values for these time intervals and their ratio, measured in the control beat, were subtracted from respective measurements in the postpremature beat to provide the respective changes in the pre-ejection period (ΔPEP), ejection time (ΔET), their ratio (Δ{PEP/ET}), and total electromechanical systole (ΔEMS).

Critique on methods

The use of fluid-filled catheters for recording the left ventricular and aortic pressures introduces error in the measurement of the pre-ejection period, and, hence, pre-ejection period/ejection time ratio and electromechanical systole, while leaving ejection time unaffected. Since the level of aortic end-diastolic pressure is not dependent on the time lag of the aortic catheter, the adopted definition for the termination of the pre-ejection period indicates that the error (prolongation) in pre-ejection period depends only on the transmission delay of the left ventricular catheter-transducer system. If the measured pre-ejection period, true pre-ejection period, and left ventricular catheter system transmission delay in the control beat were represented as PEPc, PEPc′, and Dc, and in the postpremature beat as PEPx, PEPx′, and Dx, respectively, then:

$$PEPc' = PEPc - Dc \tag{1}$$

$$PEPx' = PEPx - Dx \tag{2}$$

Subtracting (2) from (1) results in:

$$PEPc' - PEPx' = PEPc - PEPx - (Dc - Dx)$$

$$\text{or } \Delta PEP' = \Delta PEP - (Dc - Dx) \tag{3}$$

If the transmission delay in the control and the postpremature beat were assumed to be the same, that is $Dc = Dx$, then equation (3) yields $\Delta PEP' = \Delta PEP$, which means that though values for pre-ejection period (and also PEP/ET and EMS) would be somewhat increased, their changes between control and postpremature beat (ΔPEP, Δ(PEP/ET), ΔEMS) would remain unaltered. Since correlation here involved changes in, rather than absolute values of, these intervals, the catheter system delay was ignored.

The assumption that $Dc = Dx$ can be challenged on grounds of different left ventricular pulse transmission velocity in the postpremature beat whose faster rising left ventricular pressure in systole betrays the presence of a higher degree of harmonics in comparison to the control beat. The magnitude of error stemming from the acceptance of this assumption could be calculated by Fourier analysis of the left ventricular pressure signal and the frequency response of the catheter system. Our laboratory is not equipped to perform this analysis. Consequently the assumption $Dc = Dx$ was accepted on the basis of two considerations: (1) The error would probably be small. Thus, a 20% faster transmission velocity in the postpremature beat through a left ventricular catheter with, for example 10 ms delay, would introduce a 2 ms error in ΔPEP; and with unaltered ejection time the error would be similar in the case of Δ(PEP/ET) and smaller in the case of ΔEMS. An error of this magnitude is still smaller than the estimated ±5 ms error associated with manual measurement of any time interval at a paper speed of 100 mm/s. (2) The results and conclusions would only be applicable to similarly measured time intervals, based on the same assumption.

Statistical analysis

The least square method for linear regression analysis was used to correlate each of these changes with the left ventricular aortic pressure gradient in the control beat (Gc), the postpremature beat (Gx), and the change in gradient (ΔG) between control and the postpremature beat. All time intervals are rounded to the nearest millisecond. All values are reported as mean ± standard deviation..

Results

These are listed in detail in Table 1. A statistical matrix is presented in Table 2, and typical examples of the effect of postextrasystolic potentiation on systolic time intervals are shown in Fig. 1 and 2.

In comparison to the control beat, the pre-ejection period on the postpremature beat was found to be shorter in 73 instances and unaltered in the remaining two instances. The amount of abbreviation was $\Delta PEP = -20 \pm 11$ ms ($p<0{\cdot}001$), and ranged from 0 to −50 ms. For the ejection time, a prolongation was noted in all 75 instances between the control and the postpremature beat. The amount of prolongation was $\Delta ET = 37 \pm 20$ ms ($p<0{\cdot}001$), ranging from 0 to 85 ms. Without exception, the pre-ejection period/ejection time ratio in the postpremature beat was significantly ($p<0{\cdot}001$) lower than in the control beat by $\Delta(PEP/ET) = -0{\cdot}10 \pm 0{\cdot}05$ (range: −0·01 to −0·25). The change in total electrochemical systole in response to the postextrasystolic potentiation was $\Delta EMS = 18 \pm 22$ ms ($p<0{\cdot}001$).

The left ventricular outflow systolic pressure gradient rose from $Gc = 35{\cdot}6 \pm 38{\cdot}9$ mmHg (range: 0 to 130 mmHg) in the control beat to $Gx = 87{\cdot}8 \pm 69{\cdot}3$ mmHg (range: 0 to 224 mmHg) in the postpremature beat, a significant increment of $\Delta G = 52{\cdot}2 \pm 38{\cdot}9$ mmHg (range: 0 to 146 mmHg).

There was poor correlation between either ΔPEP or Δ(PEP/ET), and the gradients Gc, Gx, and ΔG (Table 2). In contrast, significant ($p<0{\cdot}001$) linear correlations were found between ΔEMS and either Gc ($r=0{\cdot}483$), Gx ($r=0{\cdot}728$), or ΔG ($r=0{\cdot}813$); and also between ΔET and either Gc ($r=0{\cdot}426$), Gx ($r=0{\cdot}720$), or ΔG ($r=0{\cdot}855$). The linear regression line relating ΔET and Δ was (Fig. 3):

$$\Delta G = 1{\cdot}65\ \Delta ET - 9$$

where ΔG and ΔET are expressed in mmHg and ms, respectively.

The Brockenbrough sign,[11] a decrease in aortic pulse pressure in the first postpremature beat as compared with the control sinus beat, was seen in only 60% (45/75) of postextrasystolic potentiation events. The sign was consistently present in nine patients (36%) and consistently absent in eight patients (32%). In the remaining eight patients (32%) it was present in some postextrasystolic potentiation events and absent in others, during the same study.

Discussion

In patients with hypertrophic cardiomyopathy, the lack of correlation between symptoms,[12] rhythm disturbances,[13] and mortality,[14] on the one hand, and

Table 1 *Response of pressures and systolic time intervals to postextrasystolic potentiation in 25 subjects (two studied twice) with hypertrophic obstructive cardiomyopathy*

Study No.	*Event No.*	*Coupling ratio*	*LVP (mmHg)*		*AoP (mmHg)*		*G (mmHg)*		*PEP (ms)*		*ET (ms)*		*ΔG (mmHg)*	*ΔPEP (ms)*	*ΔET (ms)*	*Δ(PEP/ET)*	*ΔEMS (ms)*
			C	*PPB*	*C*	*PPB*	*C*	*PPB*	*C*	*PPB*	*C*	*PPB*					
1	1	0·66	121/13	148/20	94/62	92/56	27	56	105	75	270	285	29	−30	15	−0·13	−15
2	1	0·74	116/14	116/12	103/75	94/63	13	22	140	110	260	280	9	−30	20	−0·15	−10
	2	0·73	108/16	115/17	98/71	93/62	10	22	140	110	260	290	12	−30	30	−0·16	0
	3	0·53	108/15	119/18	98/70	89/57	10	30	130	80	260	280	20	−50	20	−0·21	−30
	4	0·64	110/9	121/19	103/77	99/65	7	22	140	90	240	270	15	−50	30	−0·25	−20
	5	0·57	110/16	115/16	98/71	86/58	12	29	110	100	270	280	17	−10	10	−0·05	0
3	1	0·64	127/20	154/17	120/64	107/50	7	47	140	120	310	340	40	−20	30	−0·10	10
	2	0·73	137/17	146/24	117/57	117/64	20	29	140	130	320	330	9	−10	10	−0·05	0
	3	0·66	131/18	141/23	118/55	121/58	13	20	130	130	320	340	7	0	20	−0·03	20
	4	0·70	132/14	166/21	127/73	108/62	5	58	130	120	310	360	53	−10	50	−0·09	40
	5	0·67	131/18	142/25	114/55	111/53	17	31	140	130	320	340	14	−10	20	−0·06	10
	6	0·80	142/15	145/21	126/70	119/60	16	26	130	130	320	330	10	0	10	−0·02	10
4	1	0·53	160/38	236/36	94/56	88/48	66	148	90	80	300	340	82	−10	40	−0·06	30
	2	0·51	200/28	320/34	122/74	96/59	78	224	110	85	330	400	146	−25	70	−0·12	45
	3	0·52	194/34	304/34	106/64	96/56	88	208	95	85	330	395	120	−10	65	−0·07	55
	4	0·68	206/34	284/32	98/60	88/58	108	196	95	90	355	400	88	− 5	45	−0·04	40
	5	0·66	202/38	292/32	96/62	94/58	106	198	95	85	335	390	92	−10	55	−0·06	45
	6	0·54	218/36	306/32	112/72	96/56	106	210	100	90	340	390	104	−10	50	−0·06	40
	7	0·56	208/30	318/34	112/72	94/56	96	224	110	100	340	410	128	−10	70	−0·08	60
5*	1	0·58	121/15	125/15	110/66	97/51	11	28	120	90	260	270	17	−30	10	−0·13	−20
6	1	0·49	156/25	270/26	134/74	108/54	22	162	95	75	270	355	140	−20	85	−0·14	65
	2	0·63	172/24	246/25	146/79	128/64	26	118	100	75	275	330	92	−25	55	−0·13	30
	3	0·80	164/24	242/30	140/76	130/68	24	112	100	75	270	325	88	−25	55	−0·14	30
7	1	0·62	108/9	141/10	101/52	94/52	7	47	120	100	260	320	40	−20	60	−0·15	40
8	1	0·65	122/7	148/9	122/62	106/54	0	42	140	110	350	380	42	−30	30	−0·11	0
9	1	0·85	153/17	165/20	140/84	136/79	13	30	100	100	300	310	17	0	10	−0·01	10
10	1	0·57	162/26	228/27	140/86	108/64	22	120	120	80	270	320	98	−40	50	−0·19	10
11	1	0·67	115/23	124/27	109/67	100/58	6	24	120	90	270	280	18	−30	10	−0·12	−20
	2	0·81	115/22	124/28	113/68	114/68	2	10	110	100	260	270	8	−10	10	−0·05	0
	3	0·78	122/28	139/32	116/72	92/60	6	47	100	90	280	300	41	−10	20	−0·06	10
	4	0·65	127/22	130/30	127/80	110/65	0	20	110	90	280	290	20	−20	10	−0·08	−10
12**	1	0·89	152/18	144/16	152/60	144/57	0	0	110	110	300	310	0	0	10	−0·02	10
13	1	0·69	193/22	239/32	114/94	100/79	79	139	100	70	270	330	60	−30	60	−0·16	30
	2	0·66	202/22	246/26	126/87	122/73	76	124	90	60	270	310	48	−30	40	−0·14	10
	3	0·67	205/36	238/34	136/94	118/73	69	120	90	60	270	320	51	−30	50	−0·14	20
14	1	0·65	250/8	324/16	125/67	108/50	125	216	100	75	280	320	91	−25	40	−0·13	15
	2	0·70	243/8	311/12	123/68	105/55	120	206	110	90	300	340	86	−20	40	−0·11	20

15†	1	0·73	194/10	244/6	110/70	96/69	84	148	130	110	340	380	64	−20	40	−0·09	20
	2	0·55	222/10	260/16	126/76	106/66	96	154	130	120	350	400	58	−10	50	−0·07	40
	3	0·65	202/10	252/8	150/92	124/74	52	128	135	115	310	380	76	−20	70	−0·14	50
16	1	0·74	116/20	130/21	112/52	97/40	4	33	100	90	290	300	29	−10	10	−0·04	0
	2	0·66	109/11	122/27	101/45	114/47	8	8	105	75	285	300	0	−30	15	−0·12	−15
17	1	0·89	126/14	136/14	108/46	108/48	18	28	100	100	300	310	10	0	10	−0·01	10
	2	0·48	126/10	216/16	112/50	86/38	14	130	110	80	290	360	116	−30	70	−0·16	40
	3	0·51	130/14	208/14	112/52	86/36	18	122	100	90	300	360	104	−10	60	−0·08	50
18	1	0·48	126/10	182/18	126/60	112/58	0	70	140	110	290	340	70	−30	50	−0·16	20
	2	0·51	164/20	164/20	130/76	106/54	24	58	130	110	280	320	34	−20	40	−0·12	20
	3	0·51	128/14	136/18	128/75	124/56	0	12	130	100	290	310	12	−30	20	−0·13	−10
	4	0·62	126/11	130/18	126/72	130/64	0	0	130	110	290	300	0	−20	10	−0·08	−10
	5	0·49	118/6	166/16	118/68	104/52	0	62	140	110	280	330	62	−30	50	−0·17	20
19	1	0·56	244/20	304/18	152/80	114/58	92	190	90	70	310	360	98	−20	50	−0·10	30
	2	0·61	245/22	300/18	156/84	120/60	89	180	90	70	310	350	91	−20	40	−0·09	20
	3	0·70	222/20	284/20	170/90	130/68	52	154	90	80	290	340	102	−10	50	−0·07	40
	4	0·69	206/20	290/24	160/90	130/68	46	160	90	70	290	350	114	−20	60	−0·11	40
	5	0·61	220/20	276/22	158/84	136/68	62	140	100	70	290	330	78	−30	40	−0·13	10
	6	0·75	221/14	300/24	151/81	129/67	70	171	100	90	300	350	101	−10	50	−0·07	40
	7	0·70	220/18	266/26	154/80	146/73	66	120	90	80	280	310	54	−10	30	−0·06	20
	8	0·71	217/17	276/24	154/81	134/68	63	142	90	70	290	330	79	−20	40	−0·10	40
20	1	0·55	246/10	288/30	126/84	118/72	120	170	120	95	285	335	50	−25	50	−0·14	25
	2	0·69	260/26	304/32	130/82	112/66	130	192	125	105	300	350	62	−20	50	−0·12	30
21†	1	0·61	128/18	157/28	120/71	109/60	8	48	155	125	290	340	40	−30	50	−0·16	20
22	1	0·87	120/15	141/18	120/74	109/68	0	32	135	125	280	310	32	−10	30	−0·08	20
	2	0·88	130/20	146/19	110/72	109/63	20	37	130	120	300	320	17	−10	20	−0·05	10
23	1	0·66	137/24	167/19	105/72	96/64	32	71	120	110	330	360	39	−10	30	−0·05	20
24	1	0·64	138/9	130/8	138/67	117/50	0	13	170	140	290	305	13	−30	15	−0·13	−15
	2	0·63	129/4	133/11	129/64	113/64	0	20	160	130	280	310	20	−30	30	−0·15	0
	3	0·59	130/6	130/7	130/59	106/48	0	24	160	130	290	320	24	−30	30	−0·14	0
	4	0·64	120/4	136/10	120/60	104/47	0	22	160	130	290	330	22	−30	40	−0·16	10
	5	0·57	136/5	142/11	136/65	111/50	0	31	160	130	280	320	31	−30	40	−0·14	10
	6	0·55	130/8	144/8	130/62	106/48	0	38	150	125	280	315	38	−25	35	−0·14	10
	7	0·73	140/8	131/7	140/70	131/55	0	0	150	140	300	310	0	−10	10	−0·05	0
25	1	0·58	149/7	163/18	118/63	110/52	31	53	100	80	300	320	22	−20	20	−0·08	0
26	1	0·59	134/15	134/23	113/65	95/57	21	39	130	110	300	330	18	−20	30	−0·10	10
27	1	0·51	121/18	207/22	111/72	98/57	10	109	110	90	310	390	99	−20	80	−0·12	60
	2	0·62	126/20	206/22	102/68	94/54	24	112	115	100	320	400	88	−15	80	−0·11	55

* and ** = Mean left ventricular-aortic pressure gradient during isoprenaline infusion: 30 and 94 mmHg, respectively.

† = Repeat cardiac catheterisation.

Abbreviations: LVP, left ventricular pressure (systolic/end-diastolic); AoP, aortic pressure (systolic/diastolic); G, peak systolic LVP-AoP gradient; PEP, pre-ejection period; ET, ejection time; C, control beat; PPB, first postpremature beat; ΔG, ΔPEP, ΔET, Δ(PEP/ET), and ΔEMS, change in G, PEP, ET, PEP/ET, and electromechanical systole, respectively, between control and postpremature beat.

Table 2 *Statistical matrix relating left ventricular outflow pressure gradients and postextrasystolic changes in systolic time intervals in hypertrophic cardiomyopathy*

	ΔPEP (−20±11) (ms)	*ΔET (37±20) (ms)*	*Δ(PEP/ET) (−0·10±0·05)*	*ΔEMS (18±22) (ms)*
Gc (35·6±38·9 mmHg)	r=0·151	r=0·426*	r=0·109	r=0·483*
Gx (87·8±69·3 mmHg)	r=0·100	r=0·720*	r=−0·002	r=0·728*
ΔG (52·2±38·9 mmHg)	r=0·028	r=0·855*	r=−0·112	r=0·813*

Unmarked values for correlation coefficient (r) are statistically insignificant ($p>0{\cdot}05$).
Abbreviations: same as in Table 1.
*$p<0{\cdot}001$.

resting left ventricular outflow pressure gradient, on the other, has cast doubt on the importance of the gradient either as a determinant of the severity of the disease or as a suitable target for specific treatment. Accordingly, the usefulness of measuring the gradient seems to be limited, except as a means of confirming the diagnosis. Other aspects of the disease, however, have been found to correlate with the presence and magnitude of the gradient (for example, incidence of bacterial endocarditis[14]). Furthermore, there is no information concerning the relation between any of the aforementioned attributes and the responsiveness of the gradient to positive inotropic stimulation, which is precisely what this method determines. Because of these considerations, we believe that information on the gradient and its response to provocation is welcome, particularly if it could be procured by non-invasive means.

The systolic gradient between the left ventricular and aortic pressures found in hypertrophic cardiomyopathy has been traditionally attributed to dynamic left ventricular outflow "obstruction",[15 16] though it can also be produced by left vertricular cavity "obliteration".[17 18] Despite the fact that the postextrasystolic prolongation of ejection time invariably noted in this study represents a very strong argument supporting the "obstruction" theory, our use of the term "obstruction" need not be construed as denial of the existence of the phenomenon of "obliteration", at least in some patients. This study was not designed to provide evidence for or against either the "obstruction" or the "obliteration" theory. Instead, we attempted to establish whether the effect of the post-

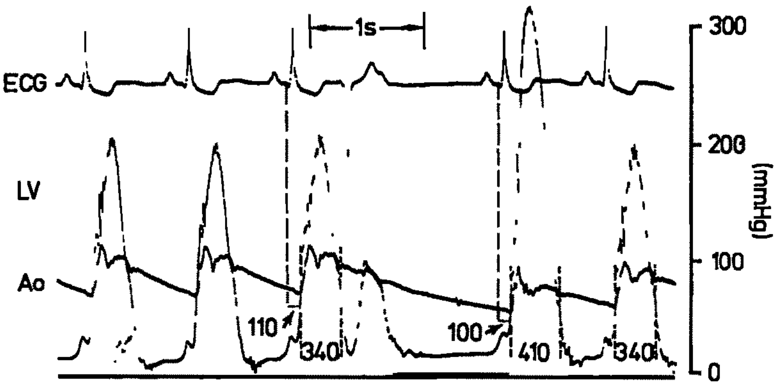

Fig. 1 *Simultaneous recording of electrocardiogram (ECG), and pressures from the left ventricle (LV) and aorta (Ao) in case 4. Note significant prolongation (70 ms) of ejection time, associated with a large (128 mmHg) change in gradient from control to postpremature beat. In this and the following figure the three vertical dashed lines on each cardiac cycle indicate, respectively, the onset of Q wave, and the onset and termination of ejection time. Values for pre-ejection period and ejection time are also shown. The ECG and LV pressure signals were retouched for clarity.*

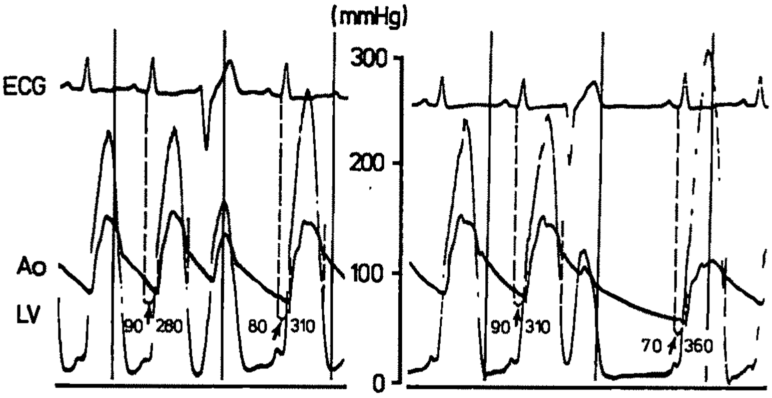

Fig. 2 *Recordings from case 19.* Left: *a modest (30 ms) prolongation in ejection time and a 10 ms abbreviation in pre-ejection period are seen, associated with a 58 mmHg increase in gradient from the control to the postextrasystolic beat.* Right: *later during same catheterisation. Note severe (50 ms) prolongation in ejection time and 20 ms abbreviation in pre-ejection period, in association with significant (98 mmHg) increase in gradient in response to postextrasystolic potentiation. The left ventricular and aortic pressure signals were retouched, and a dP/dt and pulmonary "wedge" pressure signals were removed for clarity. Abbreviations same as in Fig. 1.*

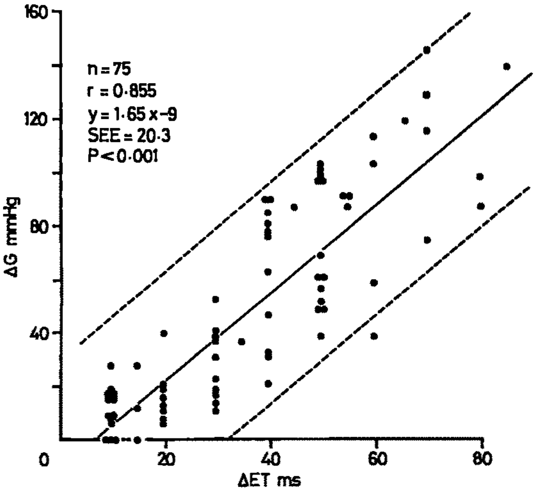

Fig. 3 *The relation between prolongation in ejection time (ΔET) and change in ventricular aortic pressure gradient (ΔG) observed in 75 instances of postextrasystolic potentiation in 25 patients. The solid line is the regression line whose equation is given. The dashed lines are drawn two standard errors of estimate (SEE) from regression line and define a confidence interval of 95%. n, number of observations; r, correlation coefficient; P, level of statistical significance.*

extrasystolic potentiation on the systolic time intervals provides quantitative information on the left ventricular outflow pressure gradient, and its responsiveness to provocation, whatever their haemodynamic or clinical significance might be.

The phenomenon of postextrasystolic potentiation has been extensively studied.[8 19–24] In comparison with the control beat, the first postpremature beat is a "stronger" beat, caused mainly, if not exclusively,[23 24] by the enhanced left ventricular inotropic state and to a lesser extent, if at all, by the increased preload and diminished afterload associated with the long postextrasystolic pause. It should be noted that the role of the Starling's effect in the postextrasystolic potentiation phenomenon remains controversial since a statistically significant increase in end-diastolic volume in the potentiated beat has been found by some[21 22] but not all[23 24] investigators. As a result of this combination, the first postpremature beat is characterised by an abbreviated pre-ejection period resulting from the left ventricular pressure rising at a faster rate (dP/dt) to travel the diminished end-diastolic difference between left ventricular and aortic pressure. This response of the pre-ejection period to the postextrasystolic potentiation has been previously observed by us in the unobstructed left ventricle, whether normal or failing,[9] and was also seen in the ventricle with dynamic left ventricular obstruction, in this series.

The effect of postextrasystolic potentiation on the duration of left ventricular ejection varies according to the presence or absence of failure and the existence and nature of obstruction to left ventricular ejection, and can be explained by reference to similar experience from the use of other positive inotropic agents.[25–27] Because of the aforementioned combination of increased left ventricular inotropic state and possibly preload, and the diminished afterload at the onset of ejection, the potentiated beat is characterised by an increased velocity of fibre shortening (ejection rate) which tends to abbreviate the duration of ejection, and by an increased extent of fibre shortening (stroke volume) which tends to prolong the ejection time. In the absence of obstruction to left ventricular ejection, the effect of increased ejection rate predominates and the ejection time shortens or, at least, remains unchanged in the potentiated beat.[9] The opposite, however, may occasionally be the case with the unobstructed but severely failing ventricle where the substantial increase in stroke volume prevails and results in a prolongation in the ejection time.[9 27]

In the case of the nonfailing but obstructed ventricle the effect of postextrasystolic potentiation on the duration of ejection is somewhat different. First, the compliance of chronically obstructed ventricles is so diminished that prolongation of diastole beyond normal makes little or no difference to their end-diastolic volume. Second, the end-systolic volume of these ventricles is usually too small to permit a substantial increase in stroke volume by way of a more complete left ventricular emptying in the potentiated beat. As a result, the longer postextrasystolic pause and the increased contractility associated with postextrasystolic potentiation do not translate into a substantial increase in stroke volume in such ventricles. This has been shown in patients with hypertrophic cardiomyopathy whose stroke volume in the potentiated beat was found to be slightly larger,[28] the same,[29 30] or even smaller,[29 30] as compared with other sinus beats. Given the augmented ejection rate of the potentiated beat, no prolongation of ejection would be expected from such modest changes in stroke volume, were it not for the presence of obstruction to left ventricular outflow with its prolonging effect on the duration of left ventricular ejection.

Although several investigators have studied the effect of certain pharmacological interventions on the duration of ejection in hypertrophic cardiomyopathy we could find only two reports containing observations on the effect of postextrasystolic potentiation on ejection time. In one of these reports a prolongation in ejection time in excess of 20 ms was found in the first postpremature beat over control, in all nine patients with provocable left ventricular outflow obstruction determined by carotid pulse morphology, by mitral valve echocardiogram or, in three patients, by pressure recording at catheterisation.[31] Because of the small number of catheterised patients, no attempt was made to correlate the prolongation in ejection time with the left ventricular outflow pressure gradient or change in gradient in the postpremature beat. In the other study, a prolongation in ejection time in excess of 20 ms was observed in the first postpremature beat in 11 of 12 patients with hypertrophic cardiomyopathy; in the exceptional patient, no change in ejection time was noted.[32] In agreement with these two studies we found prolongation in ejection time in the first postpremature beat in all our patients, ranging from 10 to 85 ms. In addition, we found a significant correlation between the amount of prolongation in ejection time and the magnitude of both the left ventricular outflow pressure gradient in the postpremature beat and the change in gradient in response to this provocation. The fact that such correlation was not found in the series of White and Zimmerman[32] could possibly be explained on the basis of two methodological differences between their study and ours. The first difference is the exclusion from our study of patients with mild to moderate left ventricular failure (ejection fraction 0·30–0·50); inasmuch as left ventricular failure is known to affect independently the response of ejection time to postextrasystolic potentiation, the inclusion of such patients in White and Zimmerman's study may have weakened the correlation. The second difference is the larger number of our observations.

Patients with small or no resting pressure gradient but with a large gradient elicited by provocative manoeuvres are likely to develop gradients under non-basal conditions such as the upright posture, muscular exercise, and the spontaneous fluctuations in the amount of circulating catecholamines and, therefore, should not be considered as having a benign form of the disease, at least as far as the left ventricular systolic function is concerned. In fact, in some institutions, their management is the same as that reserved for a patient with severe gradient at rest.[33] Therefore, severe prolongation in ejection time in the postpremature beat in a patient with hypertrophic cardiomyopathy indicates the potential for development of severe obstruction under non-basal conditions, and may provide guidance on the need and extent of treatment specifically directed against it.

In conclusion, this study has shown that in hypertrophic cardiomyopathy, postextrasystolic potentiation results in a significant prolongation in left ventricular ejection time. This prolongation is directly related to the magnitude of both the left ventricular outflow gradient of the potentiated beat and the change in gradient induced by this inotropic intervention. Given the close correspondence between internally and externally measured systolic time intervals,[34] the results of this study provide the background for the non-invasive assessment of hypertrophic cardiomyopathy from the response of external systolic time intervals to spontaneous or externally-induced premature contractions.[35]

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Relation of P–S$_4$ interval to left ventricular end-diastolic pressure

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SUMMARY Reports have suggested that the interval between P wave onset and the fourth heart sound (P–S$_4$ interval) reflects changes in left ventricular myocardial stiffness. We made simultaneous measurements of the P–S$_4$ or atrial electrogram to S$_4$ (A–S$_4$) interval and left ventricular pressure in 19 patients with coronary artery disease who were studied before and after atrial pacing. Thirteen patients developed angina accompanied by significant rises in their end-diastolic pressure and a consistent decrease in P–S$_4$ or A–S$_4$ interval; whereas the six patients who had atrial pacing without the development of angina had no changes in end-diastolic pressure, P–S$_4$, or A–S$_4$ interval. The resting data showed an inverse correlation between left ventricular end-diastolic pressure and the P–S$_4$ interval. In addition, the P–S$_4$ interval let us discriminate between patients with normal and abnormal end-diastolic pressure (>15 mmHg).

Although the fourth heart sound (atrial sound) was first described almost 100 years ago by Potain,[1] its clinical significance remains controversial. Traditionally, the atrial sound has been felt by some to be a reliable physical sign of ventricular dysfunction.[2–5] Others, however, felt that the mere presence of an atrial sound was of little diagnostic value, since it was frequently recorded by phonocardiograms in normal patients as well as in those with ventricular dysfunction.[6 7] The temporal relation of the atrial sound to the electrocardiogram and first heart sound (S$_1$) has been found to vary with clinical changes in patients with ischaemic heart disease and hypertension.[8–10]

Altered left ventricular pressure volume relations have been implicated as the common denominator in the production of the pathological fourth heart sound.[4 5] More specifically, it has been postulated that decreasing left ventricular distensibility (as reflected by increased left ventricular end-diastolic pressure) is associated with decreasing P wave to atrial sound interval (P–S$_4$) and that it is this mechanism which leads to changes in the P–S$_4$ interval.[4 10–13] It has been shown by McLaurin *et al.*,[14] Barry *et al.*,[15] and Mann *et al.*[16] that increased left ventricular end-diastolic pressure during pacing-induced angina is the result of altered left ventricular diastolic stiffness and left ventricular systolic performance during ischaemia.

We performed simultaneous phonocardiography and left ventricular pressure measurements and then used atrial pacing in patients with coronary disease to study the relation of atrial activation, timing of S$_4$ generation, and left ventricular pressure at end-diastole.

Methods

Nineteen normovolaemic patients ranging in age from 29 to 68 years were studied. All 19 patients had coronary artery disease but none had a history of chronic hypertension or electrocardiographic criteria for ventricular hypertrophy. These patients were selected because (1) they were to undergo routine cardiac catheterisation for evaluation of their presumed cardiovascular disease state, and (2) they had a fourth heart sound that could be recorded by phonocardiography. A fourth heart sound was defined as a phonocardiographically-recordable low frequency vibration occurring more than 70 ms after the onset of the P wave on the electrocardiogram.

After informed consent was obtained, cardiac catheterisations were performed with patients in the fasting state. The patients were premedicated with diazepam 10 mg orally. A 7·2 French pigtail angiocatheter (Cook) was inserted via the femoral

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artery and positioned in the left ventricle. Pressures were recorded through the fluid-filled angiocatheter connected with either a Statham P23Db transducer, or a Micron MP15 pressure transducer. The Statham pressures were electronically filtered at 12 Hz; the pressures recorded using the Micron system were hydraulically filtered with a tuned connecting system which gave a linear amplitude response to 15 Hz. For the purposes of this study, a normal left ventricular end-diastolic pressure was taken as <15 mmHg and a raised left ventricular end-diastolic pressure as >15 mmHg. A No. 6 bipolar pacing catheter was inserted via a sheath into the femoral vein to position the tip of the catheter against the right atrial wall in 12 patients using a method similar to that of Barry *et al.*[15]

To test whether the P wave onset (as seen on the surface electrocardiogram) was an accurate indicator of atrial depolarisation for the purposes of this study, the remaining seven patients underwent an identical procedure with a quadripolar pacing catheter instead of the bipolar device. When positioned on the right atrial wall, two electrodes served as pacing leads and two as sensing leads.

Phonocardiograms were obtained from all patients in the supine position with a Maico contact microphone secured at the cardiac apex with a strap. Phonocardiograms were performed with an Irex Continutrace 101 recorder and filtered through an Irex 150–102 heart sound module. The phonocardiograms were recorded using low frequency filters (50–250 Hz) with a gentle roll-off (6 decibels per octave).

The limb lead on the electrocardiogram with the longest PR interval was sought and was most commonly lead II. The electrocardiogram was scrutinised to assess the P wave onset and the lead in which this was best seen was monitored. The P wave onset was defined as a consistent deviation from the baseline noted on 50 mm/s recordings from this lead. By observing the slower speed tracing, the P wave onset could be defined consistently on 100 and 200 mm/s recordings despite less clear-cut deviations from the baseline at these speeds.

The electrocardiogram, left ventricular pressure, and phonocardiogram were recorded simultaneously in the resting state at 50, 100, and 200 mm/s paper speed (Fig. 1). The right atrium was paced with step-

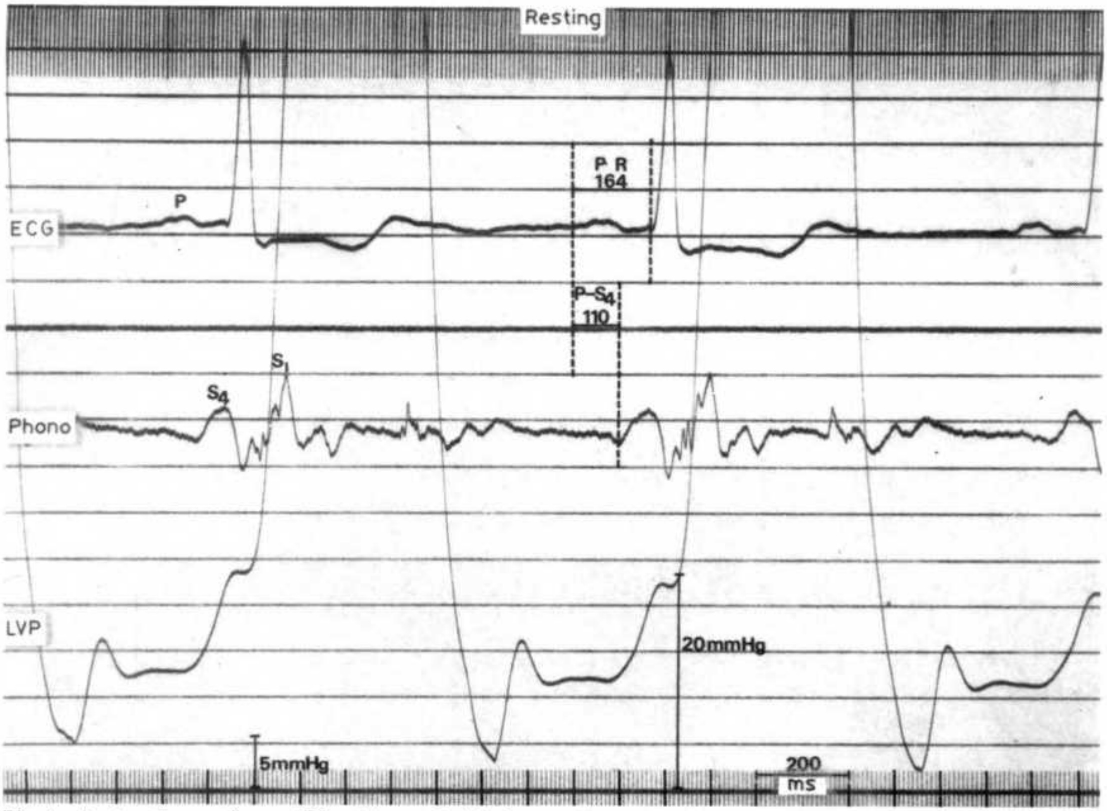

Fig. 1 *Resting phonocardiogram (Phono) in case 6 with electrocardiogram (ECG) and left ventricular pressure (LVP) showing a P–S₄ interval (P–S₄) of 110 ms, a PR interval (PR) of 164 ms, and a left ventricular end-diastolic pressure of 20 mmHg. P, P wave; S₄, fourth heart sound; S₁, first heart sound.*

wise increases in heart rate in order to induce angina pectoris. When either definite angina was induced, or the heart rate reached 150 beats/min for three minutes, the pacing was abruptly terminated, with return of the heart rate to control level. Beginning 15 to 30 seconds after cessation of pacing, at a time when angina (if induced) was still present, the electrocardiogram, electrogram (in seven patients), ventricular diastolic pressure, and phonocardiogram were simultaneously recorded again at 50, 100, and 200 mm/s paper speed (Fig. 2).

The resting and post-pacing data were analysed for (1) the interval between the onset of the P wave on the electrocardiogram or atrial depolarisation on the electrogram and the positive deflection of the main low frequency component of the fourth heart sound on the phonocardiogram; (2) the post-"a" wave left ventricular end-diastolic pressure; (3) heart rate, and (4) PR interval. The post-"a" wave left ventricular end-diastolic pressure was taken at that point (approximately 50 mm/s after the QRS onset) where the oscilloscope beam trace thinned and changed its slope toward the major systolic ventricular pressure rise. Often this was quite clear because of a plateau before the major pressure rise.

For all interval and pressure determinations the average of at least four consecutive cardiac cycles was used. The first five to six beats after termination of atrial pacing were not used for analysis, as the left ventricular end-diastolic pressure does not stabilise until after this initial post-pacing period.[17] Statistical methods used χ^2, linear regression, and multiple regression analysis where appropriate.

Results

Table 1 summarises the resting and post-pacing data obtained for the left ventricular end-diastolic pressure, P–S₄ interval, PR interval, heart rate, and development of angina pectoris in the 12 patients with only the surface electrocardiogram recorded. Table 2 displays similar data for the seven patients with atrial depolarisation to S₄ (A–S₄) interval determinations. PR, AV (interval between atrial and ventricular

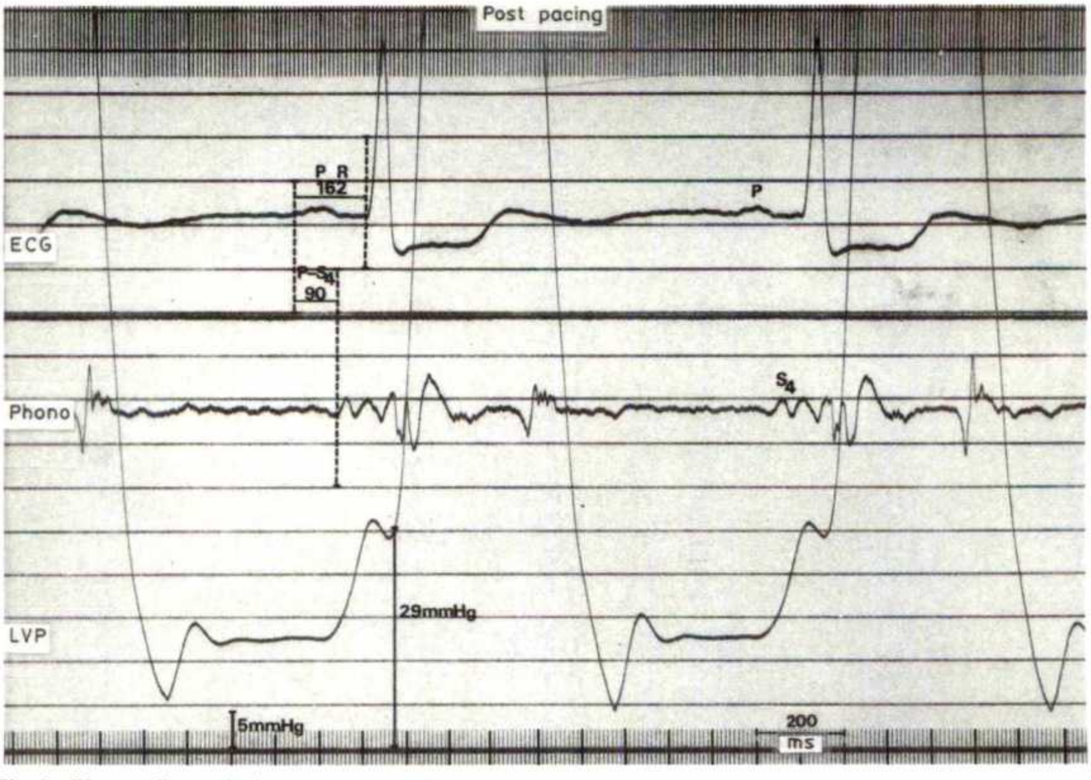

Fig. 2 *Phonocardiogram in the same patient and format as Fig. 1 showing a reduced (as compared to the resting value) immediate post-pacing P–S_4 interval (P–S_4) of 90 ms. The post-pacing PR interval (PR) of 162 ms is virtually unchanged from the resting P–R interval. Note the increase in ST segment depression which occurred during pacing-induced angina. Other abbreviations as in Fig. 1.*

Table 1 *Patient data*

Case No.	*Pacing*	*Angina*	*LVEDP*		*P–S₄ interval (ms)*		*PR interval (ms)*		*Heart rate (beats/min)*	
			Before pacing	*After pacing*	*Before pacing*	*After pacing*	*Before pacing*	*After pacing*	*Before pacing*	*After pacing*
1	Yes	Yes	8	11	141	133	128	133	93	93
2	Yes	Yes	8	14	154	149	138	141	64	65
3	Yes	Yes	18	37	128	95	156	159	75	76
4	Yes	Yes	8	31	164	119	200	199	74	75
5	Yes	Yes	31	42	134	127	148	150	75	76
6	Yes	Yes	20	29	110	90	164	162	61	61
7	Yes	Yes	30	35	95	80	146	150	82	80
8	Yes	Yes	10	15	152	136	164	162	84	86
9	Yes	Yes	12	17	140	95	130	134	96	98
10	Yes	No	12	13	165	167	213	216	72	74
11	Yes	No	11	11	136	138	145	146	73	70
12	Yes	No	17	18	109	110	138	138	73	75
Mean			16·1†	25·8†	135·3†	113·8†	155·8‡	157·5‡	76·8‡	77·4‡
Standard deviation			9·3†	11·5†	21·9†	24·3†	25·3‡	24·6‡	10·0‡	10·2‡
P value*			<0·005		<0·005		NS		NS	

LVEDP, left ventricular end-diastolic pressure.
*P value obtained by Student's paired t test.
†Statistics derived from those patients who developed angina with pacing.
‡Statistics derived from all patients.

Table 2 *Patient data, A–S₄ interval*

Case No.	*Angina with pacing*	*LVEDP (mmHg)*		*A–S₄ interval (ms)*	
		Before pacing	*After pacing*	*Before pacing*	*After pacing*
1	Yes	15	21	132	107
2	Yes	6	14	151	118
3	Yes	7	11	142	130
4	Yes	14	22	134	110
5	No	20	21	118	114
6	No	12	12	144	142
7	No	13	12	136	132
Mean		12·4	16·1	136·7	121·9
Standard deviation		4·4	4·6	9·75	12·03
P value*		<0·01		<0·02	

A–S₄, interval between atrial depolarisation and fourth heart sound.
*Student's paired t test, patients developing angina.

depolarisation on atrial electrogram), and heart rate did not change significantly after pacing in either group.

Fig. 3 shows an inverse correlation of the P–S₄ interval and the left ventricular end-diastolic pressure with a correlation coefficient of −0·727 (F = 14·5, $p<0·005$) by multiple regression analysis. In addition, multiple regression analysis showed no significant correlation between the P–S₄ interval and the PR interval (F = 1·372, $p<0·5$), nor was there any significant relation between the PR interval and the left ventricular end-diastolic pressure (F = 0·001, $p<0·975$). Fig. 4 shows the addition of the post-pacing P–S₄ interval and left ventricular end-diastolic pressure data and confirms the correlation ($r = -0·672$, $p<0·001$) between the two variables. As shown in Table 1, nine of the 12 patients (without electrogram) developed angina pectoris during pacing. These nine patients had a significant decrease in P–S₄ interval ($p<0·005$) and a significant increase in their ventricular end-diastolic pressure ($p<0·005$) compared with pre-pacing values. In contrast, the other three patients who were paced, but did not develop angina, had no significant change in their P–S₄ interval in relation to left ventricular end-diastolic pressure. The change in the P–S₄ interval in relation to the left ventricular end-diastolic pressure was ΔP–S₄/Δ left ventricular end-diastolic pressure = 2·8 ms/mmHg. As also seen in Table 1, there was no significant change in resting as compared with post-pacing heart rates or PR intervals. In addition, there was no significant change in the post-pacing left ventricular systolic pressure.

The results for the seven patients with atrial electrograms were similar to those with surface electrocardiogram only. Fig. 5 illustrates the values for such a patient before (resting) and after pacing. The A–S₄ interval correlated closely with left ventricular end-diastolic pressure for both the resting and post-pacing conditions (Fig. 6). Four of the seven patients developed angina during pacing; these subjects displayed significant ($p<0.02$) increases in left ventricular end-diastolic pressure and corresponding decreases in A–S4 interval. As in the surface electrocardiogram subjects, PR interval, AV interval (atrial to ventricular depolarisation interval), and intrinsic heart rate did not change after pacing. P wave to atrial electrogram interval did not change after pacing.

Discussion

The atrial sound has been the subject of considerable controversy in regard to its pathophysiology and clinical significance.[3 6 7 11] In an excellent review, Craige[11] has put this controversy into perspective and concluded: (1) the basic mechanism involved in the production of the atrial gallop is exaggerated left ventricular stiffness during the time of atrial systole, and (2) the atrial gallop is a valuable sign of altered left ventricular function. The present study examines the temporal relation of the P–S4 interval to two basic variables: (1) the PR interval of the electrocardiogram, and (2) left ventricular end-diastolic pressure possibly reflecting left ventricular diastolic stiffness. It is important to note that (1) in the post-pacing record there was no significant change in PR interval or heart rate as compared with the resting data, and (2) there was no significant correlation between the P–S4 interval and the PR interval or heart rate in our study group.

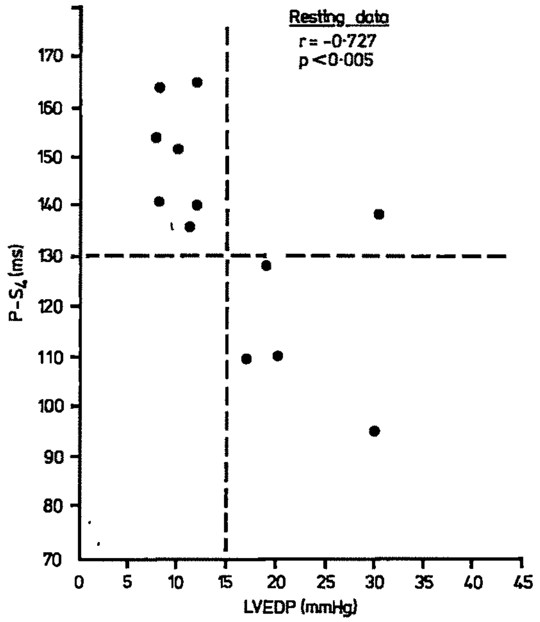

Fig. 3 *Correlation of resting P–S4 interval (P–S4) and left ventricular end-diastolic pressure (LVEDP) for the 12 patients not having atrial electrograms are shown. The vertical dashed line indicates the border of abnormal left ventricular end-diastolic pressure (>15 mmHg) and normal pressures (≤15 mmHg). The horizontal dashed line divides the P–S4 interval into two zones of interest.*

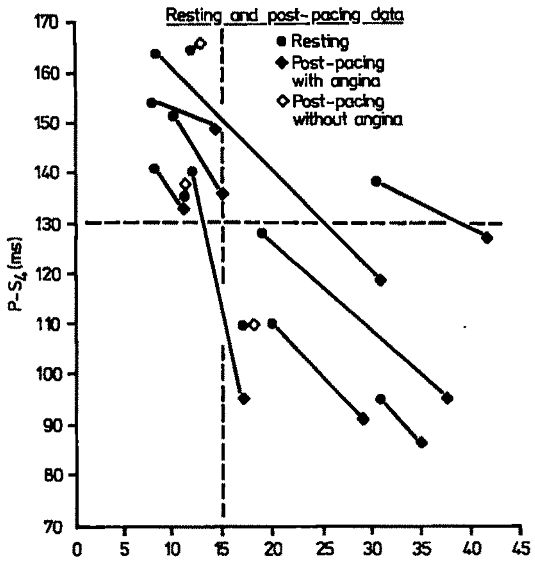

Fig. 4 *Plot showing resting and post-pacing P–S4 interval (P–S4) versus left ventricular end-diastolic pressure (LVEDP) with data on angina development in the 12 patients of Fig. 3.*

Although left ventricular end-diastolic pressure is an imperfect index of left ventricular diastolic stiffness, Mirsky and co-workers[18] found a good correlation between left ventricular diastolic stiffness and left ventricular end-diastolic pressure in patients with coronary artery disease. The intervention of rapid atrial pacing to produce angina pectoris in patients with coronary disease increases left ventricular end-diastolic pressure primarily as a result of increasing left ventricular diastolic stiffness.[14–17] Thus, we may choose to view the range of left ventricular end-diastolic pressures in the resting condition and the increment during pacing-provoked angina as reflecting differing states of ventricular stiffness altered by ischaemia.

The present study showed an inverse relation between the P–S4 or A–S4 interval and left ventricular end-diastolic pressure in the resting state. The 13 patients with coronary artery disease who had atrial pacing-induced angina pectoris then showed an increase in left ventricular end-diastolic pressure and a consistent decrease in their P–S4 or A–S4 interval, with each patient serving as his own control. This suggests that the P–S4 and A–S4 interval are related to

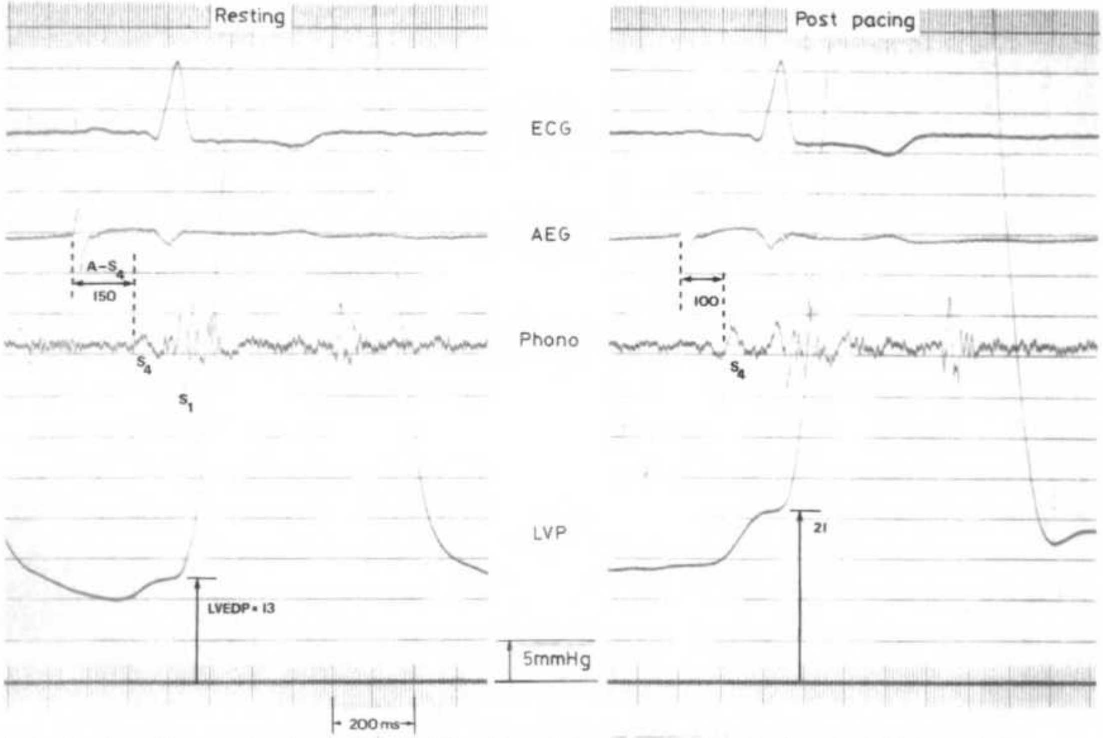

Fig. 5 *Resting and post-pacing phonocardiogram (Phono) [case 1 from Table 2]. Note the change in A–S_4 interval and corresponding LVEDP. Abbreviations as in Fig. 1 and 2; AEG, atrial electrogram.*

ischaemia-induced changes in the left ventricle. These findings corroborate earlier work which noted shortening of the P–S_4 interval in patients who had deterioration in their clinical status.[8–10] Also, these data are consistent with the observations of Craige[11] who has noted shortening of the P–S_4 interval when the ventricle demonstrates increased stiffness. One may postulate that the bolus of blood entering the ventricle, as a result of atrial contraction, eventually encounters forces resisting ventricular dilatation. If the ventricle is relatively stiff, then this resistance may occur abruptly and early after the P wave. Such checking of this bolus might produce the vibrations recorded as S_4. This circumstance of a stiff ventricle may be envisioned as producing raised end-diastolic pressure, as well as an "early" S_4, in response to the bolus of blood from the atrium.

The P–S_4 intervals in our study can be divided into three zones: (1) ≤ 130 ms, usually associated with abnormal left ventricular end-diastolic pressure; (2) >130 ms but <140 ms cannot clearly discriminate between normal and abnormal left ventricular end-diastolic pressure; and (3) ≥ 140 ms, usually associated with normal left ventricular stiffness as reflected by left ventricular end-diastolic pressure. The correlation between the P–S_4 interval and the left ventricular

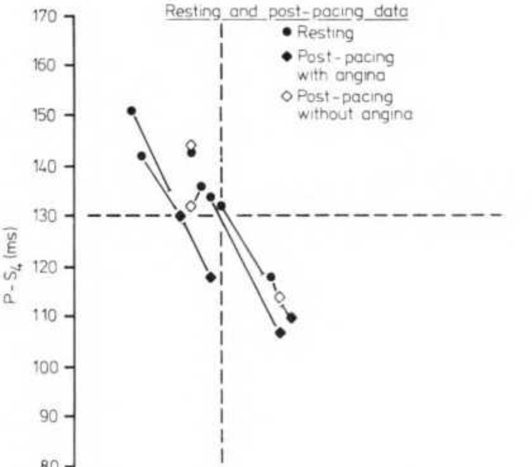

Fig. 6 *Plot showing resting and post-pacing values for the atrial electrogram of fourth sound interval (A–S_4) and left ventricular end-diastolic pressure (LVEDP) for the seven patients with atrial electrograms. Abbreviations as in Fig. 3, symbols as in Fig. 4.*

end-diastolic pressure is not adquate to attempt to quantify left ventricular end-diastolic pressure accurately. Experience with more patients will be needed to assess the limits of these categories but there were recordable fourth heart sounds in seven patients with normal left ventricular pressures in this study, and yet the temporal relations of the P wave to the fourth heart sound distinguished these patients from those with apparently abnormal left ventricular function. It is possible that our conclusions may not be applicable either to patients with extremely early diastolic P waves, very short or prolonged PR intervals, or distorted P waves caused by interatrial conduction defects.

We believe that this study clarifies previous concepts and observations concerning the pathophysiological significance of the timing of the fourth heart sound. In addition, we have documented the effects of ischaemia-induced changes in left ventricular diastolic pressure upon the P–S4 interval. These measurements may prove useful in clinical phonocardiography as a further means of non-invasive classification of left ventricular function.

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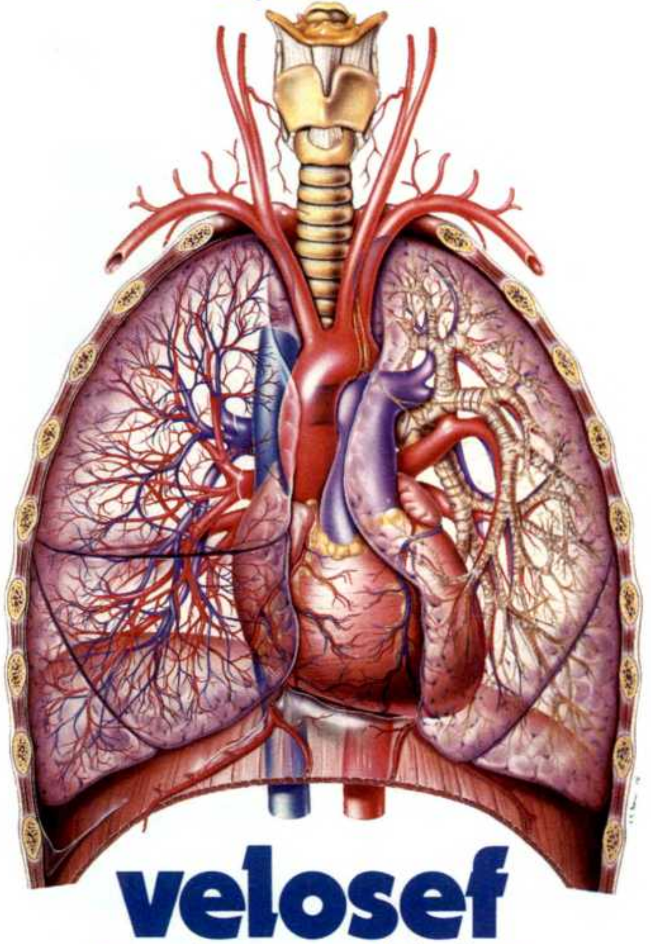

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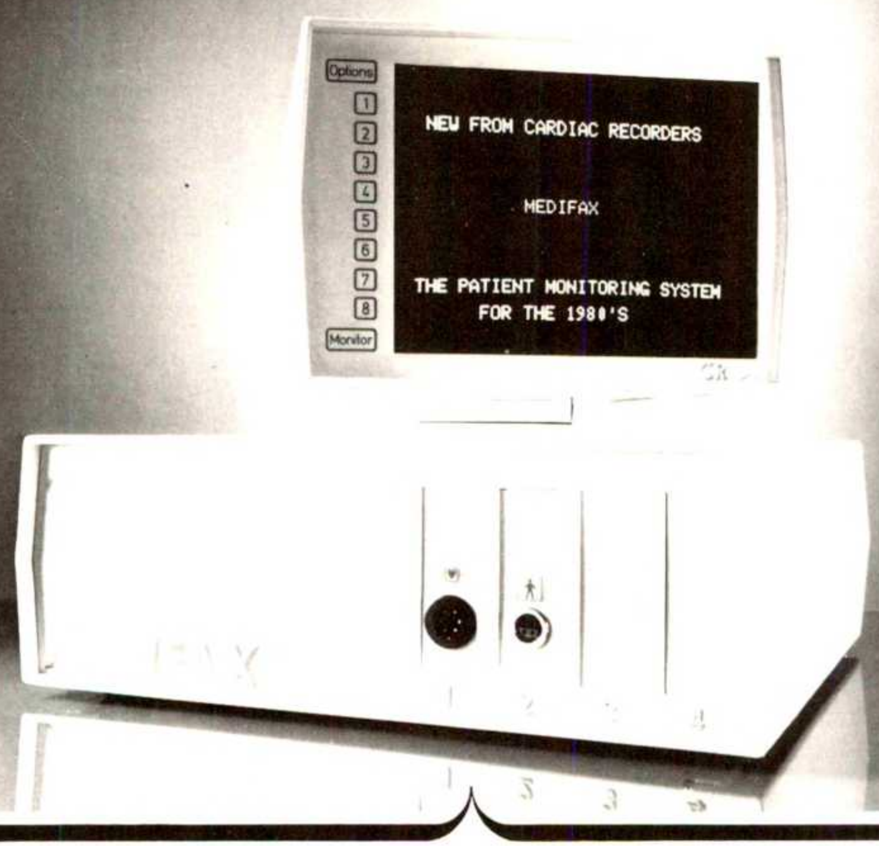

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Br Heart J 1982; **47**: 277–80

Hang-out time of pulmonary valve in d-transposition of great arteries

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SUMMARY Recently it has been shown that in patients with transposition of the great arteries the isometric relaxation time of the left ventricle could be negative in the presence of normal pulmonary artery pressure. In order to find an explanation for this apparently paradoxical situation, it was decided to evaluate the importance of the delay of closure of the pulmonary valve in 15 patients with transposition of the great arteries. This delay is called the hang-out time. The hang-out time was found to correlate inversely with the isometric relaxation time as well as with the pulmonary artery systolic ($r = -0{\cdot}70$) and mean pressures. A weaker correlation was found between the isometric relaxation time and the time of mitral valve opening. These results show that in transposition of the great arteries with normal pulmonary artery pressure, the pulmonary valve has a prolonged hang-out time, to the extent that it frequently closes after the opening of the mitral valve, explaining the negative isometric relaxation time found in these cases. This finding may help in the non-invasive assessment of the pulmonary vascular resistance of patients with transposition of the great arteries.

In a recent publication we have shown that in transposition of the great arteries the isometric relaxation period of the left ventricle, measured non-invasively, had a strong correlation with the pulmonary artery pressure.[1] The isometric relaxation time was also found to be negative in the presence of a normal pulmonary pressure, suggesting that in these circumstances the mitral valve paradoxically opens before the pulmonary valve closes. The reasons for this peculiar situation are still speculative. Early mitral opening, late pulmonary closure, or both, are obvious possibilities. The pulmonary valve is known to close sometimes after the end of ventricular ejection. This delay of closure is called the hang-out time.[2] When right ventricular and pulmonary artery pressures are simultaneously recorded by high-fidelity catheter-tipped micromanometers, the hang-out time can easily be measured and corresponds to the interval separating the pulmonary incisura from the right ventricular pressure tracing at the level of the incisura. This interval is influenced mainly by the capacitance of the pulmonary vascular bed.[2] The purpose of the present study was to investigate whether the hang-out time of the pulmonary valve of patients with transposition of the great arteries could be prolonged to the point that late pulmonary closure would be the factor responsible for the negative isometric relaxation time observed in the presence of normal pulmonary pressure.

Subjects and methods

Echocardiograms were obtained in 15 children with transposition of the great arteries aged 1 day to 5 years. All studies were done within 48 hours of cardiac catheterisation. Patients with pulmonary stenosis were excluded from the study since in these cases other factors such as stiffness of the pulmonary leaflets could affect their time of closure. Tracings were recorded simultaneously with an electrocardiogram on a Smith Kline Ekoline 20A, coupled with a Honeywell fibreoptic recorder (model 1856). Paper speed was set at 100 mm/s, allowing measurement to the nearest 5 ms. Aerotech 5 MHz unfocused and 3·5 MHz focused transducers were used, according to the size of the patients.

The left ventricular pre-ejection period was meas-

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ured from the onset of depolarisation (beginning of the Q wave on the electrocardiogram) to the opening of the pulmonary valve. The ejection time was determined by two methods: first, from opening to closure of the pulmonary valve,[3] and second, by taking the point of maximal anterior movement of the left ventricular wall as the end of ejection (E point),[4] with the ejection time as the difference between the interval Q–E and the pre-ejection period. The hang-out time was calculated as the difference between the two figures. (Fig. 1). The isometric relaxation time of the left ventricle was calculated as the difference between Q to mitral valve opening and Q to pulmonary valve closure, as previously described.[1] All measurements were done on cardiac cycles with equal preceding RR intervals. Each value represents the mean of at least five different complexes.

The relation between the hang-out time and the isometric relaxation time, as well as the pulmonary pressures, was evaluated by linear regression analysis. To appreciate the possible influence of the time of opening of the mitral valve on the isometric relaxation time, correlation between the latter and Q to mitral valve opening was also studied.

Results

Echocardiographic and catheterisation data are summarised in the Table. In five cases with no angiographic signs of pulmonary stenosis, the pulmonary artery was not entered and only left ventricular systolic pressures are given. In three of them (cases 7, 13, and 14), the absence of a gradient was confirmed at surgery. Pulmonary stenosis was also ruled out at the necropsy of case 12.

The hang-out time of the pulmonary valve was positive in nine patients (Fig. 1A) and negative in six (Fig. 1B). A strong inverse correlation was observed between isometric relaxation time and hang-out time ($r = -0{\cdot}88$, $p < 0{\cdot}001$) (Fig. 2). All patients with a negative isometric relaxation time had a positive hang-out time. Patients with a positive isometric

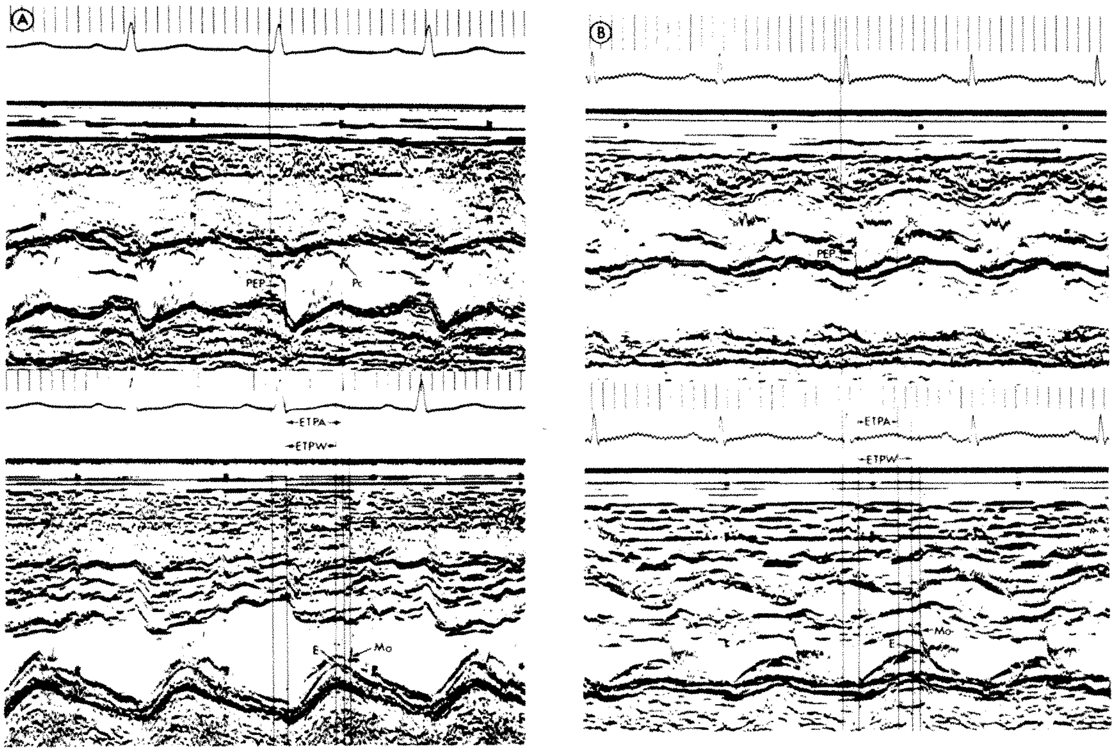

Fig. 1 *Echocardiograms of pulmonary and mitral valves of two children with transposition of the great arteries demonstrating the technique used to measure the left ventricular ejection time on the pulmonary artery (ETPA) and on the posterior wall of the left ventricle (ETPW). The hang-out time is measured by subtracting ETPW from ETPA. (A) Example of a positive hang-out time. (B) Example of a negative hang-out time. This child had severe pulmonary hypertension. Mo, mitral valve opening; Pc, pulmonary valve closure; PEP, pre-ejection period.*

Table *Echocardiographic and haemodynamic data*

Case No.	*Age*	*Associated lesions*	*ETPW (ms)*	*ETPA (ms)*	*HT (ms)*	*IRT (ms)*	*PA (mmHg) Systolic*	*Mean*
1	7 mth		200	230	30	−30	22	14
2	16 mth		200	215	15	20	17	9
3	30 mth		215	270	55	−10	36	15
4	2 d	VSD	170	180	10	10	45	32
5	33 mth		220	240	20	−15	20	11
6	2 y		225	250	25	−15	23	16
7	6 mth		225	180	−45	45	60	
8	24 mth		200	220	20	5	36	20
9	26 mth		240	250	10	10	21	16
10	24 mth		225	210	−15	40	95	77
11	12 mth	VSD	240	230	−10	45	87	65
12	26 mth		190	145	−45	90	82	
13	6 mth		220	210	−10	70	65	
14	12 mth		165	225	60	−25	30	
15	2 d	VSD	210	170	−40	55	64	

ETPW, ejection time calculated on the posterior wall of the left ventricle; ETPA, ejection time measured on the pulmonary valve; HT, hang-out time; IRT, isovolumic relaxation time; PA, pulmonary artery; VSD, ventricular septal defect.

relaxation time greater than 20 ms had a negative hang-out time. An inverse correlation was also found between the hang-out time and the systolic ($r = -0{\cdot}70$, $p < 0{\cdot}005$) (Fig. 3) and the mean ($r = -0{\cdot}78$, $p < 0{\cdot}005$) pulmonary pressures. All six patients with a negative hang-out time had a systolic pulmonary pressure higher than 60 mmHg. A positive but weaker correlation was found between the isometric relaxation time and the Q to mitral valve opening interval ($r = 0{\cdot}56$, $p < 0{\cdot}05$).

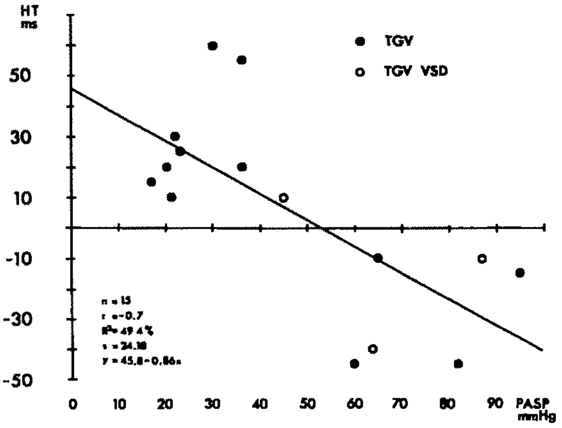

Fig. 3 *Correlation between the hang-out time (HT) and the pulmonary arterial systolic pressure (PASP).*

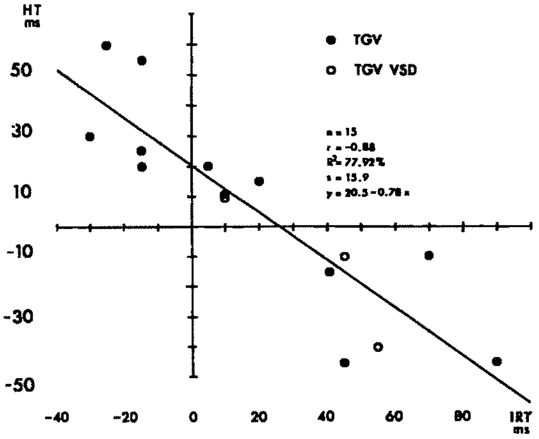

Fig. 2 *Correlation between the hang-out time (HT) and the isometric relaxation time (IRT).*

Comments

Several methods have been proposed to evaluate the left ventricular ejection time by echocardiography. The most widely used relies on the time of opening and closure of the aortic valve.[3] These two points can indeed be easily identified but this method includes the hang-out time of the valve in the ejection time of the ventricle. While in the systemic circulation the hang-out time can be considered negligible (less than 15 ms), this is, however, not the case in the normal, highly capacitant, pulmonary circulation, in which it may vary between 30 and 120 ms.[2] In most cases of transposition of the great arteries, vascular resistance is low and pulmonary flow increased. The hang-out time of the pulmonary valve can thus be expected to be in the high ranges. This could explain why left ventricular ejection time in transposition of the great arteries, measured from the pulmonary valve, has been found to be prolonged when pulmonary pressure is normal.[3 5]

Another method of measuring left ventricular ejection time, based on posterior wall systolic excursion, excludes the hang-out time. Measurements are made either from the beginning to the maximum of the systolic forward movement of the endocardium, or from the Q wave to the maximum of forward movement of the posterior wall minus 50 ms.[4] In our study, the latter method was used, the Q wave being a point easily identifiable. The standard value of 50 ms, used as the pre-ejection period of the systemic circulation, could not be used in transposition of the great arteries where the left ventricle faces the pulmonary circulation. Therefore for each case the actual pre-ejection period was subtracted from the Q–E point. This method has been shown to overestimate left ventricular ejection time.[4] The reason for this overestimation is unclear. In the present study this has probably led to an underestimation of the hang-out time and can therefore explain the negative values observed in the cases with pulmonary hypertension in which a very short hang-out time would normally be expected.[6]

While the absolute values found for the hang-out time in this study may be underestimated, this does not invalidate the correlations observed between this measurement and the isometric relaxation time or the pulmonary pressures. In transposition of the great arteries, with a normal pulmonary pressure, pulmonary vascular resistance is low and the hang-out time is prolonged to such a point that pulmonary closure occurs after mitral opening, explaining the negative isometric relaxation time found in most of these cases.[1] Variations in the latter are also correlated, but to a lesser degree, with the timing of mitral valve opening. Indeed, in this study, the mitral valve tended to open earlier in the presence of negative isometric relaxation time and normal pulmonary pressure. One can speculate that in transposition of the great arteries when the pulmonary resistance is low, the pulmonary flow is generally increased. This leads to a higher pulmonary venous return into the left atrium which could be responsible for an earlier opening of the mitral valve.

This study confirms the validity of the isometric relaxation time of the left ventricle as an index of the pulmonary pressure in transposition of the great arteries. Measurement of the hang-out time of the pulmonary valve appears to be another and much quicker means of evaluating this pressure. In routine echocardiography of patients with transposition of the great arteries, a rapid assessment of pulmonary arterial pressure can indeed be made, simply by measuring the intervals Q to the end of ejection and Q to pulmonary valve closure on two cycles with the same preceding RR intervals. In the presence of low pulmonary pressure the latter should always be longer than the former. This observation does not predict an absolute value for the pulmonary arterial pressure, but a negative hang-out time should certainly help in detecting pulmonary hypertension during the follow-up of such patients.

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Angio-pathological appearances of pulmonary valve in pulmonary atresia with intact ventricular septum

Interpretation of nature of right ventricle from pulmonary angiography

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SUMMARY Correlative angiographic-anatomical studies in 19 cases of pulmonary atresia with intact ventricular septum showed the following relations between the angiographic appearance of the pulmonary valve and the morphology of the right ventricle.

(1) Doming of the pulmonary valve was associated with a nearly normal-sized right ventricle and a wide infundibulum patent to the level of the pulmonary valve.

(2) A fixed valve was associated either with (a) pronounced hypoplasia of the ventricular chamber and stenosis of the infundibulum or (b) less commonly, a massive right ventricle and Ebstein's malformation of the tricuspid valve.

(3) An intermediate type valve was associated with a small right ventricle and a small infundibulum which was, however, patent to the level of the pulmonary valve.

It is suggested that the configuration of the pulmonary valve is a result of haemodynamic stresses placed upon it. These stresses, in turn, are determined by the morphological nature of the right ventricle. Thus, the nature of the pulmonary valve as seen angiographically may be used as an index of right ventricular morphology.

Infants with pulmonary atresia and intact ventricular septum are often critically ill and require urgent diagnosis and treatment in the neonatal period.[1] The type of operation performed, whether pulmonary valvotomy or a combination of an aorto-pulmonary shunt and the creation of an atrial septal defect, is based upon angiographic determination of right ventricular size and morphology.[2–5] Several authors have emphasised the variability of infundibular morphology and its importance in influencing the outcome of pulmonary valvotomy.[5–8] In cases where the infundibulum is patent to the level of the pulmonary valve and the atretic valve takes the form of a thin diaphragm, surgical right ventricular to pulmonary artery continuity may be obtained more readily than in those instances of severe infundibular hypoplasia or atresia.[4 5 8]

Zuberbuhler and Anderson[6] recently described the anatomical characteristics of the pulmonary valve in their necropsy specimens of pulmonary atresia with intact ventricular septum; there were two distinct appearances. In the first type, "prominent commissural ridges converged and met at the centre of the 'valve'", while in the second type the commissural ridges were "present only at the periphery of the membranous pulmonary valve, the centre being smooth and bulging into the pulmonary trunk". Additionally, they found that the first type of pulmonary valve "was invariably associated either with infundibular atresia or with a severely stenotic or regurgitant tricuspid valve". Using this as a basis, we have attempted to correlate the angiographic appearance of the pulmonary valve, not only with its anatom-

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ical appearance, but also with the underlying right ventricular and infundibular morphology. Such a correlation, if available, would be of considerable clinical interest, since it would distinguish between infants in whom pulmonary valvotomy alone might be inadequate to establish right ventricular to pulmonary arterial continuity and those in whom continuity could be easily established and right ventricular growth encouraged.

The purpose of this study, therefore, was to determine whether the angiographic character of the pulmonary valve in cases of pulmonary atresia with intact ventricular septum was a reliable basis from which to predict the size and morphology of the right ventricular chamber.

Subjects and methods

The following observations were made: (1) the nature of the pulmonary valve as seen in angiocardiograms; (2) the nature of the pulmonary valve in necropsy specimens; (3) the size and morphology of the right ventricular chamber in angiocardiograms; and finally (4) the size and morphology of the right ventricle and tricuspid valve in necropsy specimens.

To determine the nature of the pulmonary valve angiographically, use was made of the lateral views of those left ventriculograms, aortograms, or the late phase of venous angiograms that showed the base of the pulmonary trunk. Angiograms from 27 patients were available for review, and in 19 of these the base of the pulmonary trunk was clearly seen angiographically (nine aortograms, four left ventriculograms, three pulmonary arteriograms performed after aortopulmonary shunting procedure, one left atriogram, and two late phase venous angiograms). In the other eight patients in whom angiography had been done, the pulmonary valve was not well visualised because of either an insufficient amount of contrast material (an aortogram in two patients) or the fact that the valve was obscured by overlying cardiac structures (forward angiograms in six patients). In the 19 satisfactory angiograms, the pulmonary valve was classified angiographically by one of us (AGF) as domed, fixed, or an intermediate form. This part of the study was done with the knowledge that pulmonary atresia with intact ventricular septum was present but without that of other details of the cases.

A domed valve was identified when, during ventricular systole, the valve plate was mobile and formed either a large domed or box-like bowing into the pulmonary trunk. Pulmonary valve sinuses were often visible at the base of the dome. With *a fixed valve*, the base of the pulmonary trunk did not change in shape during the cardiac cycle and consistently appeared as a "pouch". Pulmonary valve sinuses were identified in some but not all cases. *An intermediate form of the valve* was present when doming, though present, involved only a small central portion of the valve plate. Well-formed valve sinuses were visible at the base of the pulmonary trunk.

Ten of the 19 patients with satisfactory angiograms had eventually died. Using the eight necropsy specimens available from these cases we compared the angiographic characteristics of the pulmonary valve with its anatomical appearance. In five specimens the pulmonary valve had not been operated upon. In two specimens (each with a fixed valve), an eccentrically placed single incision pulmonary valvotomy had been performed but each of these two valves could be easily reapproximated and the details of the anatomy determined. In the final necropsy specimen (that with a domed valve), though a small portion of pulmonary valvular tissue had been surgically removed, it appeared that sufficient tissue remained intact in order to classify the valve.

The size and morphology of the right ventricle were determined by at least one of the following methods in each of the 19 cases: right ventriculography (15 cases), necropsy (eight cases), at operation (one case). In five cases both the right ventriculogram and the necropsy specimen were available.

The available right ventriculograms were analysed for the presence and size of the infundibulum, the presence of myocardial sinusoids, the size of the inflow portion of the right ventricle, and the presence of tricuspid regurgitation.

In the eight necropsy specimens, the diameter of the infundibular chamber was measured by calibrated sound. Right ventricular and left ventricular inlet and outlet dimensions were measured as previously described[6] and were compared with previously published age-related normal values.[9] A right ventricular/left ventricular index was obtained by multiplying right ventricular inlet and outlet dimensions and dividing this product by the product of left ventricular inlet and outflow dimensions.[6]

Difficulties were encountered in measuring the very smallest ventricles with confidence. Though we remeasured these chambers on subsequent occasions and were satisfied that we could reproduce our figures, it is possible that the size of the very smallest right ventricles has been overestimated because of the presence of myocardial sinusoids in these specimens.

The circumference of the true tricuspid valve annulus was measured in each case and compared with previously published age-related normal values.[9] The circumference of the pulmonary trunk immediately proximal to its bifurcation was measured in each specimen.

The tricuspid valve was examined where possible in each of the eight specimens for Ebstein's malformation and for dysplasia of the valve. Tricuspid valve dysplasia was characterised as previously described by Becker and associates[10] and included focal or diffuse thickening of the valve leaflets, deficient development of chordae and papillary muscles, improper separation of the valve components from the ventricular wall, and focal agenesis of valvular tissue.

Results

DOMED PULMONARY VALVE

In four of the 19 angiocardiographic studies (cases 1 to 4) the pulmonary valve appeared "domed" (Fig. 1a). The central part of the valve plate was mobile and smooth and bulged forward into the pulmonary trunk during ventricular systole. The angiographic appearance of the valve was similar to classical critical pulmonary valvular stenosis except that a jet was not identified. Necropsy in two of the four patients with domed valves who died showed the pulmonary valve to have the following characteristics (Fig. 1b).

The atretic pulmonary valve plate was thin and dome-shaped. On its arterial aspect were three shallow, thick, equidistant raphes, each terminating at the central part of the plate. Three well-formed sinuses were present.

The circumferences of the pulmonary trunks were 18 and 20 mm, respectively.

Three of the four patients with a domed pulmonary

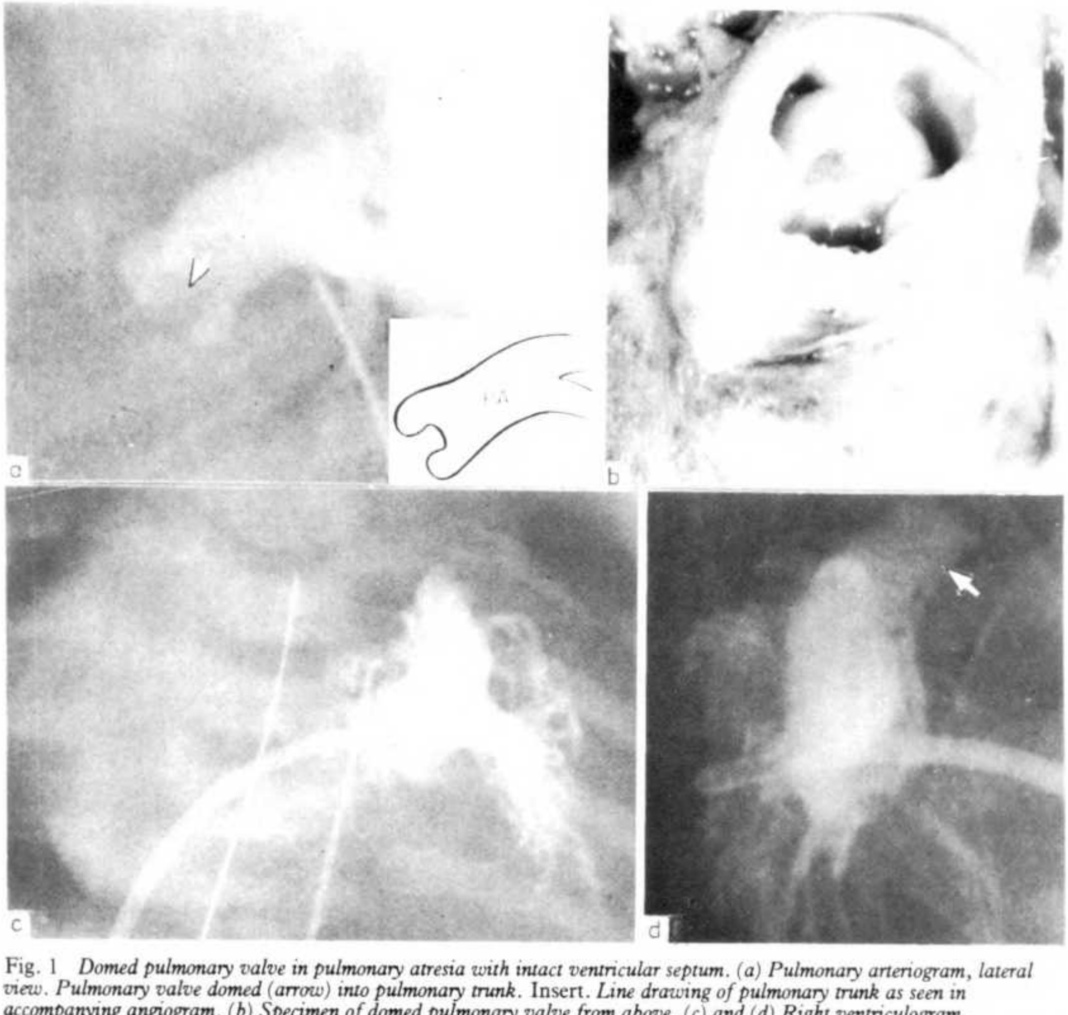

Fig. 1 *Domed pulmonary valve in pulmonary atresia with intact ventricular septum. (a) Pulmonary arteriogram, lateral view. Pulmonary valve domed (arrow) into pulmonary trunk.* Insert. *Line drawing of pulmonary trunk as seen in accompanying angiogram. (b) Specimen of domed pulmonary valve from above. (c) and (d) Right ventriculogram, anteroposterior view (c) and lateral view (d). Right ventricle smaller than normal. Infundibulum patent to level of pulmonary valve (arrow).*

valve had had right ventriculograms. In each, the right ventricular inflow portion was highly trabeculated and of nearly normal size. "Significant" tricuspid regurgitation was present in each, though part of this regurgitation may have been catheter-induced. Myocardial sinusoids were not seen. The infundibulum was of normal calibre and appeared patent to the level of the pulmonary valve in each case (Fig. 1c and d).

In the two available necropsy specimens with a domed pulmonary valve, analysis of the right ventricle disclosed the following characteristics. The infundibulum admitted a 2 to 3 mm probe, and the probe could be advanced to the pulmonary valve. Right and left ventricular dimensions were within the limits of normal for age,[9] but the right ventricular/left ventricular indices of 0·58 and 0·81 disclosed the relative hypoplasia of the right ventricle in these cases (Fig. 2).

The circumference of the tricuspid valve annulus in both specimens was below the average age-related value.[9] Neither specimen showed gross evidence of Ebstein's malformation, but both showed signs of dysplasia, consisting of focal thickening of the leaflets and shortened chordae.

FIXED PULMONARY VALVE

Angiograms of nine patients (cases 5 to 13) showed the pulmonary valve to be of the "fixed" type (Fig. 3a). The pulmonary arterial root retained a pouch-like shape throughout the cardiac cycle, and no doming of the valve was seen. Five patients in this group died, and necropsy specimens were available in four of these cases. In each specimen the base of the pulmonary trunk appeared primitive and poorly defined (Fig. 3b). The valve plate was a flat firm membrane. Upon its arterial aspect two or three thin ridges converged to meet at the centre of the valve plate. The pulmonary valve sinuses were poorly formed.

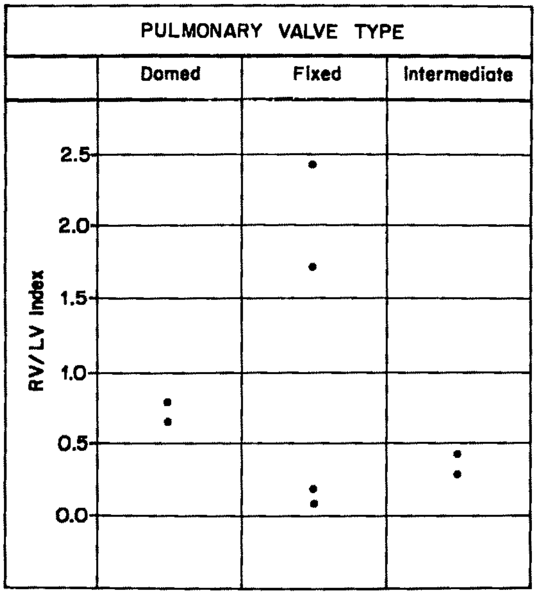

Fig. 2 *Right ventricular/left ventricular indices determined for all necropsy specimens with pulmonary atresia and intact ventricular septum. Cases grouped by valve type.*

The circumference of the pulmonary trunk ranged from 14 to 24 mm.

In seven of the nine patients with a fixed valve, a right ventriculogram was available. From these, two distinct types of ventricular morphology were found. In two patients the right ventricle was much enlarged and associated with massive tricuspid regurgitation (Fig. 4a and b). The infundibular chamber in each was widely patent, and myocardial sinusoids were not demonstrated. In each of the other five patients with a fixed pulmonary valve the right ventricular chamber was minute and the infundibulum tiny. Myocardial sinusoids were prominent in each case, and tricuspid regurgitation was minimal or absent (Fig. 4c and d).

Necropsy specimens were available in four of the patients with a fixed pulmonary valve. In each of the two cases with an enlarged right ventricle the infundibulum was a poorly defined extension of the body of this chamber. Measured right ventricular dimensions exceeded the limits of normal for age-related controls, while left ventricular dimensions were within the normal range.[9] The right ventricular/left ventricular indices of 2·45 and 1·71 (Fig. 2) indicated the degree of right ventricular enlargement. Ebstein's malformation of the tricuspid valve was present in both cases. The atrialised portion of the right ventricle was significant in each specimen. Nevertheless, in contrast to cases with isolated Ebstein's malformation, the true right ventricular chamber, as measured from the base of the abnormal tricuspid valve leaflet, was also larger than the average age-related value.[9]

The circumference of the true tricuspid annulus was obtained in each of these specimens, and in both was larger than the average age-related value.[9] In addition to Ebstein's malformation, each tricuspid valve showed signs of dysplasia, including focal thickening of the leaflets, deficient chordal development, attachment of valvular tissue directly to the right ventricular wall, and, in one case, focal agenesis of valvular tissue.

In the two remaining necropsy specimens with the angiographic appearance of a fixed pulmonary valve, the infundibulum was very stenotic, and a 2 mm probe could not be advanced into it, there being muscular obstruction between it and the pulmonary valve.

Right ventricular dimensions were abnormally small, while left ventricular dimensions were within

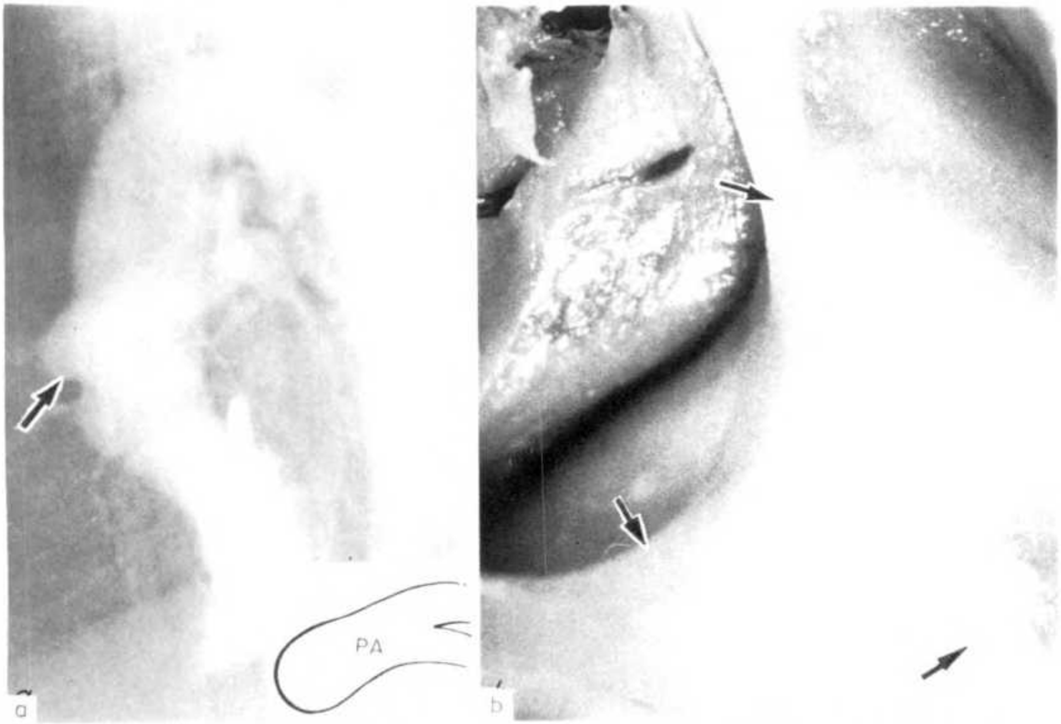

Fig. 3 *Fixed pulmonary valve in pulmonary atresia with intact ventricular septum. (a) Left ventriculogram, lateral view. Pulmonary arterial root appears as a fixed single pouch-like sac (arrow) during ventricular systole. Neither valve sinuses nor central area of doming are present.* Insert. *Line drawing of pulmonary trunk as seen in accompanying angiogram. (b) Specimen of fixed type of pulmonary valve from above. Three raphes (arrows) meet in centre of valve plate.*

normal limits and the right ventricular/left ventricular indices were 0·19 and 0·11, reflecting the extreme hypoplasia of the right ventricle (Fig. 2).

In one survivor of the group with the fixed type of valve no right ventriculogram was performed, but at operation a very hypoplastic tricuspid valve and right ventricle were seen.

The circumference of the tricuspid valve annulus was measured in each case and found to be less than the average age-related value.[9] Severe tricuspid valve dysplasia was present in both specimens and consisted of thickened valve tissue, abnormal chordae and papillary muscles, and focal agenesis of valvular tissue.

INTERMEDIATE PULMONARY VALVE

From angiograms in the remaining six cases (cases 14 to 19), the pulmonary valve was classified as of the "intermediate" type. The valve sinuses were well formed. A small area of separation was seen between the sinuses centrally. During ventricular systole the area of separation widened and the tiny central portion of the atretic valve plate domed (Fig. 5a). Three patients died, and specimens were available from two. In both, the pulmonary valve bore a strong resemblance to the domed pulmonary valve in that three thick ridges or raphes were present but did not extend to the centre of the valve plate. The central area of the valve was smooth and thin but, in contrast to the classical domed valve, formed only a small portion of the total valve surface (Fig. 5b).

The circumferences of the pulmonary trunks were 18 and 26 mm, respectively. In four of the five patients with an intermediate type of pulmonary valve, right ventriculograms were available for study. In each case the inflow portion of the right ventricle was small. The infundibulum was present and appropriate for the size of the ventricle but appeared smaller than normal (Fig. 5c and d). Myocardial sinusoids were seen in two of the right ventriculograms, but in the other two their presence could not be determined. Tricuspid regurgitation was mild in each case. Three patients from this group died, and necropsy specimens were available in two. A 2 mm probe could be advanced into each infundibulum to the level of the pulmonary valve. Right ventricular dimensions

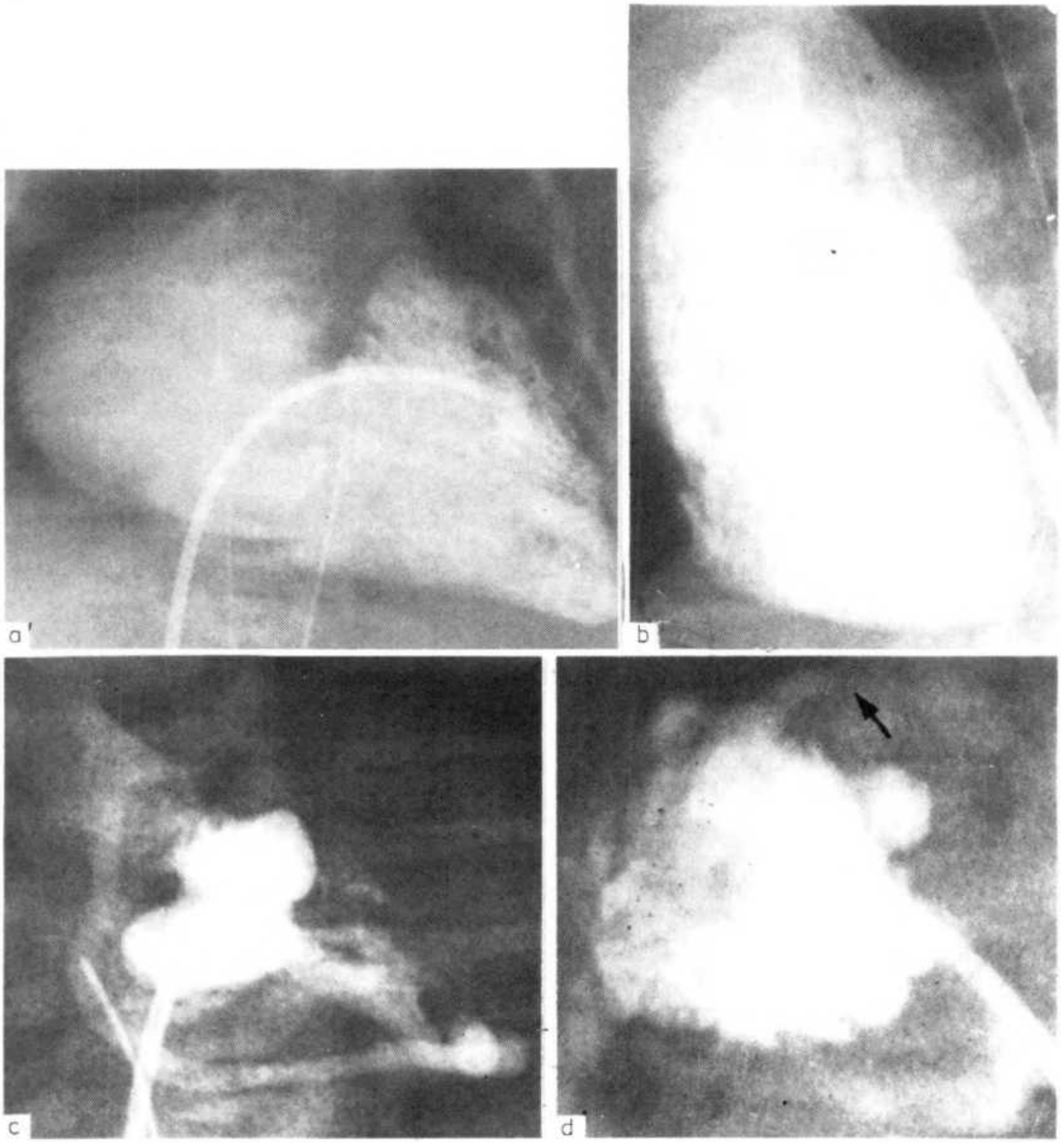

Fig. 4 *Two cases of pulmonary atresia with fixed type of pulmonary valve. (a) and (b) Enlarged right ventricle and tricuspid regurgitation. Right ventriculogram in frontal view (a) and lateral view (b). (c) and (d) Minute right ventricle. (c) Frontal view shows prominent myocardial sinusoids through which opacification of the aorta occurs. (d) Lateral view. Hypoplastic infundibulum (arrow).*

were smaller than the average age-related normal values, but left ventricular dimensions were within normal limits.[9] The right ventricular/left ventricular indices of 0·42 and 0·32 were intermediate between the values in those specimens with a tiny right ventricle and fixed pulmonary valve, and those with a nearly normal ventricular size and domed pulmonary valve (Fig. 2).

The circumference of the tricuspid valve annulus was measured in both specimens and was found to be less than the average value but still within the range of normal for age-related controls.[9] Tricuspid valve dys-

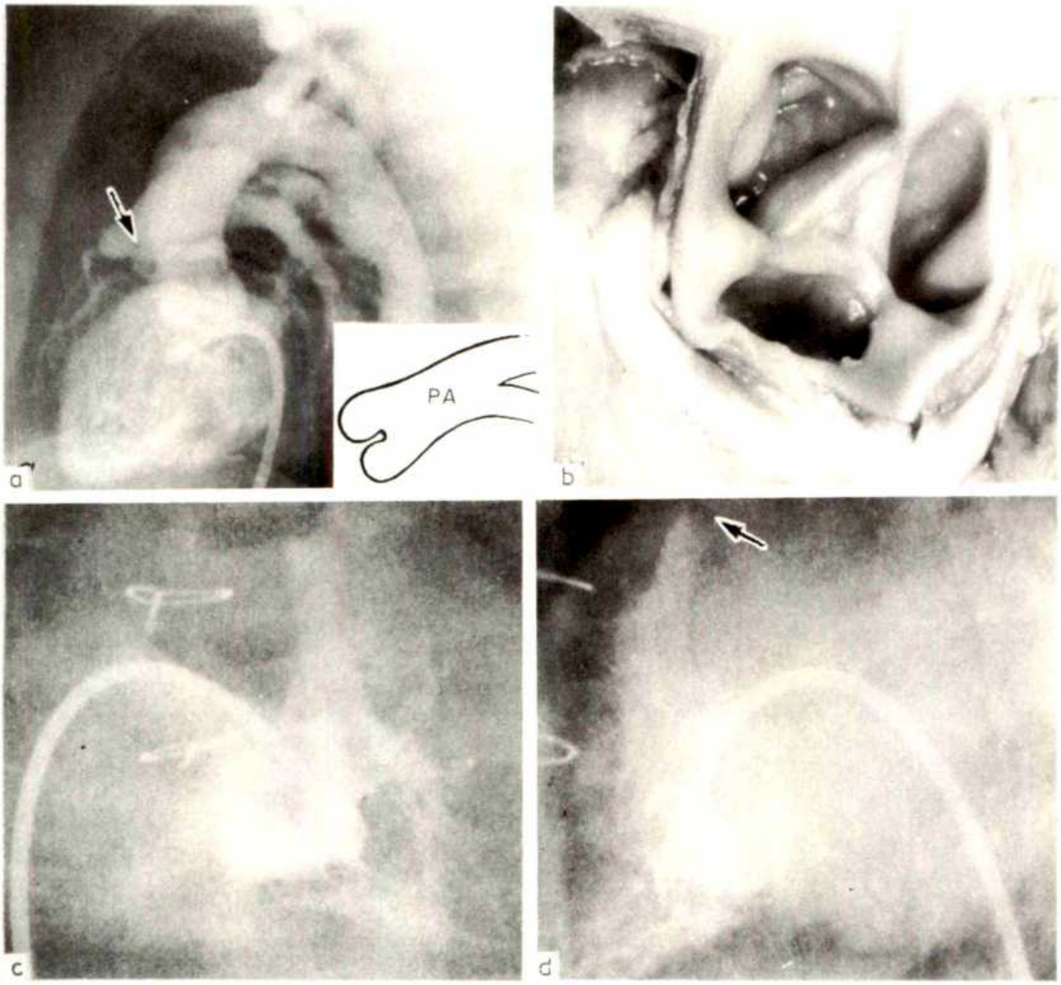

Fig. 5 *Intermediate type of pulmonary valve in pulmonary atresia with intact ventricular septum. (a) Left ventriculogram, lateral view. Two well-formed pulmonary valve sinuses are seen, the posterior sinus being partially obscured by the overlying ascending aorta and coronary artery. A tiny central dome separates the valve sinuses (point of arrow).* Insert. *Line drawing of pulmonary trunk as seen in accompanying angiogram. (b) Specimen of intermediate type pulmonary valve viewed from above. (c) and (d) Right ventriculogram, anteroposterior view (c) and lateral view (d). Right ventricle small. Infundibulum patent to level of pulmonary valve (arrow).*

plasia was present in both specimens, consisting of abnormal chordae and thickened leaflets in one case and an arcade-like tricuspid valve in the other.

Comment

This study confirmed the general concepts of Zuberbuhler and Anderson[6] that in pulmonary atresia with intact ventricular septum there is variation in the structure of the pulmonary valve and, moreover, that there is a tendency for certain structural types of pulmonary valve to be associated with particular right ventricular features.

Additionally, the direct relation between the circumference of the tricuspid valve annulus and the right ventricular chamber size reported in this study, as well as the finding of some degree of tricuspid valve dysplasia in all specimens, supports the conclusions not only of Zuberbuhler and Anderson but also of others.[11] That no correlation could be found between the pulmonary arterial size and the underlying right ventricular morphology was also in accord with previous findings.[6]

This study also showed that there is a close correlation between the angiocardiographic appearance of the pulmonary valve and the state of the valve when examined directly.

Zuberbuhler and Anderson[6] designated two structural main types of atretic pulmonary valves conforming to the types we have called the domed and fixed types. Our observations indicate that a third form may be identified angiographically, the intermediate type.

The correlation between the type of pulmonary valve, and the morphology of the right ventricle, seems to be a logical expression of the haemodynamic stresses upon the pulmonary valve caused by right ventricular anatomy. Whatever causes atresia of the pulmonary valve, it may be assumed that the condition is established early in embryonic life. Thus, stresses upon the valve plate occur for many months before birth and these stresses have an influence in moulding its structure.

Our study showed the association of the domed type of valve with a near-normal sized right ventricle and infundibulum, while tricuspid regurgitation was either absent or minimal. It is likely that under these conditions the right ventricular pressure is abnormally high, and the full force of this pressure is applied to the pulmonary valve plate, causing it to dome.

When the valve plate is of the fixed type, represented by a flat membrane, we found that the right ventricle was either large and associated with tricuspid regurgitation or the right ventricle and its infundibulum were hypoplastic. Under either of these circumstances relatively low levels of pressure would be applied to the valve plate, leaving it in a non-domed state.

The intermediate type of valve is characterised by minimal doming and in this type it is reasonable that the haemodynamics of the right ventricle are intermediate between those associated with the domed and fixed types of valve.

Thus, it appears evident that the appearance of the pulmonary valve plate is a consequence of stresses upon it, and the anatomical nature of the right ventricle determines the haemodynamics which, in turn, influence the valve configuration.

From the clinical point of view, this concept may be helpful, as from a given configuration of the pulmonary valve, subvalvular haemodynamics may be inferred. From the latter, in turn, a concept of right ventricular morphology may be assumed, though the potential for right ventricular growth after pulmonary valvotomy may also depend upon several other factors as well, including right ventricular compliance, the presence of myocardial sinusoids, and the nature of the tricuspid valve.

Although we have not used this classification in a prospective fashion, we believe, from the evidence presented, that a pulmonary valvotomy in the newborn period in an infant with a fixed type pulmonary valve should probably be avoided. In the cases where such a valve exists with a large right ventricle, tricuspid regurgitation in concert with neonatal pulmonary hypertension may, as others have noted,[6 12] result in cardiac output inadequate to sustain life. In cases where a fixed pulmonary valve exists with a tiny right ventricle, establishing continuity between the ventricle and pulmonary artery almost certainly cannot be achieved by valvotomy alone. In addition, severe tricuspid stenosis and dysplasia may preclude adequate growth and function in spite of successful right ventricular outflow tract reconstruction.

On the other hand, in cases of pulmonary atresia and intact ventricular septum where the pulmonary valve appears to be either domed or "intermediate", a valvotomy in the newborn period appears technically feasible, either alone or together with an aortopulmonary shunting procedure. In addition, right ventricular chamber size in both of these categories approaches normal values more closely and thus the potential for growth of the right ventricle may be anticipated.

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Study of children of parents operated on for congenital cardiovascular malformations

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SUMMARY The incidence of congenital cardiovascular malformation was studied in 246 children of 166 index patients who had been operated upon for this. Twelve children were affected (4·9%). More than half of these had the same malformation as the parent. The incidence of other extracardiac congenital abnormalities did not exceed that recorded in Hungary for the population in general.

The aetiology of the more common types of congenital cardiovascular malformation, for example ventricular septal defect, can best be explained on the basis of the multifactorial threshold model.[1] In Hungary, the risk of a congenital cardiovascular malformation occurring in the sibs of an affected patient was found to be about 3% for ventricular septal defect[2] and for secundum atrial septal defect.[3] These figures are in accord with previously published data.[4] Information on the risk in the children of such patients, however, is scanty, probably because of the previously low survival rate of patients with these congenital abnormalities. Because of significant advances in cardiovascular surgery in the past 25 years, the situation has changed. At present, the majority of patients with congenital cardiovascular malformations survive, with a good chance of having children, and it is therefore important to establish the risk of these having similar lesions. In early studies, Neill and Swanson[5] found the incidence to be 4·8% of the children of affected mothers and Nora *et al.*[1 6 7] 2·6 to 4·3% of the children of both affected men and women. Zetterquist,[8] Ando *et al.*[9] and, more recently, Dennis and Warren[10] have also provided data indicating a risk of approximately 3%. We report a follow up survey of the children of index patients who had undergone surgery for a congenital cardiovascular malformation.

Subjects and methods

In 1977, the names, birth dates, addresses, clinical diagnoses, and blood groups of all patients born in or before the year 1950 who had undergone surgery for a congenital cardiovascular malformation were obtained from the files of the National Institute of Cardiology, Budapest. Patients who had both cardiovascular and extracardiac abnormalities, that is identifiable or non-identifiable syndromes, were excluded from the study. Our sample consisted of 539 index patients, 210 men and 329 women. The number and sex distribution for each type of malformation are shown in Table 1. A brief questionnaire concerning family status, number and outcome of pregnancies, as well as the health of children if any, with special reference to the occurrence of cardiovascular malformations was sent to every patient. The Figure summarises the results of the survey. Sixty-five per cent of the patients responded. The relatively high proportion "not located" can be explained by the high social mobility in Hungary and by the fact that many of the patients were now independent adults and had already left home. The actual percentage of changed addresses was even higher than 20%, but we were able to find some patients with the help of the municipal council organisations. There is no reason to believe that the proportion of children found to be affected by congenital cardiovascular malformations would have been much different if we had been able to find the missing index patients. The 15% "no response" category is a better figure than usual and suggests that the patients were co-operative. In all, data were obtained on 85% of the cases we were able to find.

All children thought by their parents to have a congenital cardiovascular malformation were called to the National Institute of Cardiology for examination. Those reported as "not-affected" were referred to the regional paediatric outpatient clinic. The necropsy on the six children who had died did not indicate the occurrence of heart defects in any cases.

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Table 1 *Type of congenital cardiovascular malformations of index patients and their children*

Index patients				*Children*					
Type of congenital cardiovascular malformation	*Sex*	*No. of cases*		*No. of children*		*Type of congenital cardiovascular malformations*	*Sex*	*No. of cases*	
Ventricular septal defect (VSD)	M	18	48	10	22	—	—	0	0
	F	30		12		—	—	0	
Secundum atrial septal defect	M	70	187	10	42	CA	M	1	6
(ASD II)	F	117		32		ASD II, VSD	MMMF, F	5	
Persistent ductus arteriosus (PDA)	M	45	176	9	75	—	—	0	3
	F	131		66		PDA, ASD II	MF, M	3	
Tetralogy of Fallot	M	27	53	6	6	—	—	0	0
	F	26		0		—	—	0	
Pulmonary stenosis	M	21	33	4	8	—	—	0	0
	F	12		4		—	—	0	
Aortic stenosis (AS)	M	6	8	2	4	—	—	0	2
	F	2		2		VSD, AS	M, F	2	
Coarctation of aorta (CA)	M	21	32	4	9	—	—	0	1
	F	11		5		VSD	M	1	
Valve anomalies	M	2	2	0	0	—	—	0	0
	F	0		0		—	—	0	

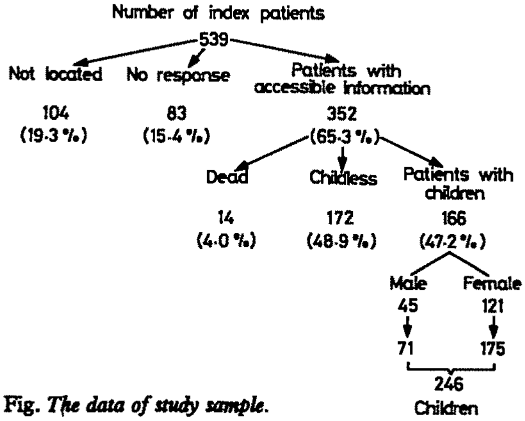

Fig. *The data of study sample.*

Results

Fourteen of the 352 index patients about whom there was information had died (Fig) and 172 did not have children (101 of them were unmarried). In all, 166 married patients had had a total of 246 children, an average of 1·48 children per patient. The patients also reported 50 unsuccessful pregnancies (Table 2). The national figures of spontaneous abortions (1·3%), ectopic pregnancies (0·2%), and stillbirths (0·8%) are not significantly different from those which had occurred. The percentage of female patients who had had a spontaneous abortion was, however, significantly higher that that in the wives of male patients ($\chi_1^2=6{\cdot}49$; $p<0{\cdot}05$), suggesting an effect of congenital cardiovascular malformation on the pregnancy itself. Nevertheless, it must be noted that men may not be a reliable source of information on this particular question.

Out of the total of 246 children in the study, 16 were thought to have a congenital cardiovascular malformation, an apparent incidence of 6·5% of live births. One hundred and fifty-one index patients had 222 healthy children, six had one affected child only, one had two affected children, and eight had one affected and one unaffected child. Fifteen of the allegedly affected 16 children underwent cardiological examination at the National Institute of Cardiology. Only seven of them were found to have a congenital cardiovascular malformation, while the remaining eight had functional or innocent murmurs without an underlying organic disorder. The child who was not brought to the institute for examination turned out to have a heart defect, previously adequately documented, and was thus considered to be "affected".

Thus, information obtained from the patients con-

Table 2 *Outcome of index patients' pregnancies*

Index patients *Outcome of pregnancy*	*Male N=45*		*Female N=121*		*Total N=166*	
	M	*Rate*	*M*	*Rate*	*M*	*Rate*
Spontaneous abortion	5	6·5%*	41	18·7%*	46	15·5%*
Ectopic pregnancy	—	0·0%*	1	0·0%*	1	0·3%*
Stillbirth	1	1·3%**	2	1·1%**	3	1·2%**
Livebirth	71	1·6†	175	1·4†	246	1·5†
Total	77	1·7†	219	1·8†	296	1·8†

*Occurrence per 100 total planned pregnancies.
**Occurrence per 100 total births.
†Livebirths or total planned pregnancies per one index patient.

cerning their children proved to be only 50% reliable and the true incidence of congenital cardiovascular malformation in those children appeared to be 3·25%.

Only 66·5% of the 230 children referred to the outpatient paediatric clinics attended for examination. This ratio is far from satisfactory. We did, however, receive information from several, but not all, of the patients concerned that their child had already been examined for cardiovascular abnormalities, and had been found to be healthy. Four of the children actually examined at the clinics were found to have a congenital cardiovascular malformation; three had a secundum atrial septal defect, and one a coarctation of the aorta. Thus, in the case of children considered to be "not-affected" parental information was 97% correct (143 of 153). Adding the above four cases to the number of affected children increased the incidence of congenital cardiovascular malformation in the children to 4·9%.

Discussion

The incidence of congenital cardiovascular abnormality of 4·9% is five times higher than that found at birth in the newborn in Hungary,[11 12] and about 1·6 times higher than that found in sibs.[2 3] This figure, furthermore, should be regarded as a minimal value since there might have been further affected children among the remaining 77 who did not attend the outpatient clinics.

Four additional points merit discussion. One of these is the similarity in many cases of the lesion in the parents and their children. The same type of malformation was observed in both parent and child in seven out of 12 cases. This clearly suggests a specific genetic factor though the remaining five children had a different malformation from their parents indicating that congenital cardiovascular malformations are not as type-specific as other congenital abnormalities.

A second point concerns the relative incidence of the different types of congenital cardiovascular malformations in the children. Our sample is not large enough to allow firm conclusions in this respect but it is worthy of note that both of the women with aortic stenosis had an affected child, one of them having aortic stenosis, and that when one parent had a secundum atrial septal defect the apparent risk of a child having a cardiac lesion was over 14% (6 out of 42). Four of these six children had the same type of defect as the parent. The mode of inheritance of atrial septal defect and atrial septal defect with atrioventricular conduction defects has been described as being by an autosomal dominant phenotype, and this particular mode of inheritance is considered definite in McKusick's[13] catalogue. If all or some of these families had secundum atrial septal defect type of autosomal dominant origin this could make the recurrence risk we found seem too high.

The third important problem is whether a distinction can be made between the genetic and the environmental factors (teratogen, maternal) in the development of congenital cardiovascular malformations. Analysis of the sex of the affected parents might be instructive. We found, unexpectedly, that in 11 of the 12 affected children it was the mother who was the original patient. In other words, among the 175 children of the 121 affected women the incidence of malformation was 6·3%, whereas among the 71 children of the 45 affected men it was only 1·4%. This difference, however, is not statistically significant ($p=0{\cdot}10$). The common types of congenital cardiovascular malformation are the most likely to correspond to the multifactorial threshold model.[14] The relatively low total recurrence rate may reflect the polygenic liability. The seemingly higher prevalence among the children of affected mothers may be the result of possible triggering effects of environmental (intrauterine) maternal factors.

Finally the prevalence of other congenital abnormalities (3·25%) was no higher than that normally found in Hungary (about 4% including congenital cardiovascular malformations).[15]

In summary, approximately 5% of children of a parent with a congenital cardiovascular malformation will have one too. Genetic counselling should call attention to this enhanced risk and patients should be advised to have their children examined by a cardiologist. As a result of our study four children with congenital cardiovascular malformation were discovered and two have already had an operation.

We thank Professor Attila Árvay and Domokos Boda for access to the data on the index patients.

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Isolated atresia of the aortic arch in a 65-year-old man
Surgical treatment and review of published reports

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SUMMARY A 65-year-old patient with isolated aortic arch atresia documented by cardiac catheterisation and cineangiography is described. Successful surgical repair was performed using a 10 mm Dacron tube graft to bypass the atretic segment.

Isolated atresia of the aortic arch is rare. In aortic arch atresia the arch is continuous, yet a segment of it is atretic so that apart from a collateral circulation, communication with the lower aortic segment is absent. Haemodynamically, the condition is similar to complete interruption of the aortic arch.

To our knowledge only 10 cases of isolated aortic arch atresia or interruption have been reported.[1-9] In eight cases, the diagnosis was confirmed at operation, one case was diagnosed but untreated,[8] and in one patient, the diagnosis was made at necropsy.[1]

In this report we present a 65-year-old man with isolated atresia of the aortic arch which was subsequently corrected by operation. The anatomical aspects, diagnostic problems, and surgical approach are discussed, with a review of the previously published cases.

Case history

A 65-year-old Bedouin man was referred to the Sheba Medical Centre for evaluation of shortness of breath, dizziness, palpitation, fatigue, and cachexia of one year's duration. On admission he was in poor general condition, cachectic, and dyspnoeic at rest. The blood pressure in the right arm was 145/120 mmHg but it could not be measured in the left arm. There was no cyanosis. Examination of the neck showed distinct enlargement of the neck veins. The right carotid artery was normal; the left carotid was palpable but very weak. The chest was symmetrical and aeration of the lungs was equal. The apex of the heart was visible and palpable in the sixth intercostal space in the anterior axillary line. Examination of the back disclosed arterial pulsation in the intercostal spaces on the right side only. The liver was enlarged 3 cm below the right costal margin and was tender to palpation. The femoral and peripheral leg pulses were not palpable bilaterally. The electrocardiogram showed sinus rhythm, enlargement of both atria, left ventricular hypertrophy, and strain. Chest *x*-ray film showed right sided rib notching. The haemoglobin was 14·7 mg/100 ml; WBC 7900; blood urea 7·0 mmol/l (42 mg/100 ml); serum creatinine 79·6 mmol/l (0·9 mg/100 ml). Cardiac catheterisation was performed via a percutaneous Seldinger right axillary approach. Thoracic aortography showed interruption of the aortic arch before the origin of the left subclavian artery (Fig. 1A and B), with late filling of the descending thoracic aorta via a collateral circulation, especially the left vertebral artery (Fig. 2A and B).

At operation a left thoracotomy was made in the fourth left intercostal space. The aorta was dissected retrogradely, freeing the left subclavian artery which was small, approximately 3 mm in diameter. Further dissection of the aortic arch disclosed a narrow, 3 mm long segment of the aorta between the left subclavian artery and the left common carotid artery; no lumen was present. The left common carotid and right brachiocephalic trunk were dissected. A 10 mm woven Dacron graft was anastomosed to the left side of the brachiocephalic trunk using partial occlusion and was connected to the distal descending thoracic aorta using the same technique (Fig. 3). After completion of the anastomoses, a mean blood pressure of 80

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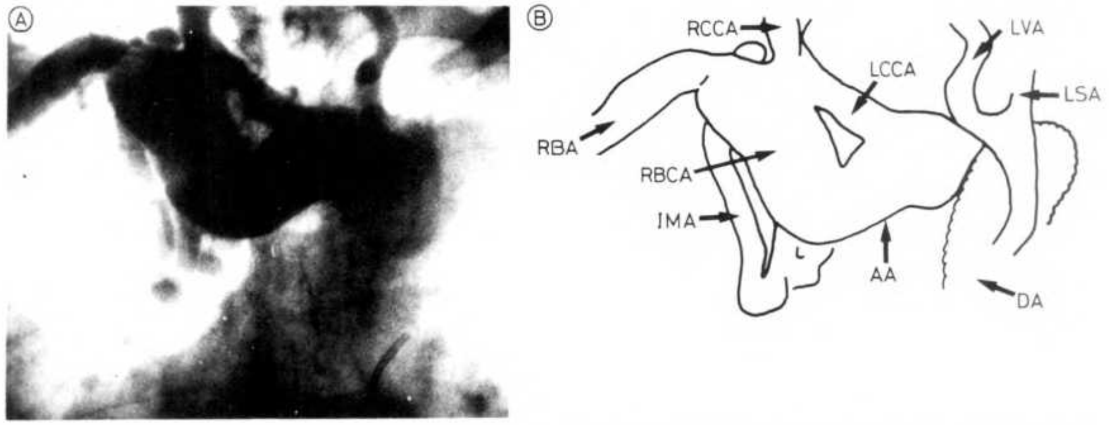

Fig. 1 *(A) The early phase of the ascending thoracic arteriogram in the right anterior oblique position. The brachiocephalic trunk is conspicuously dilated. Contrast material does not enter the descending thoracic aorta. (B) Diagrammatic representation of Fig. 1A. Contrast material introduced into the ascending aorta (AA) through the right brachial artery (RBA) flows into the right brachiocephalic artery (RBCA) and right common carotid artery (RCCA), left common carotid artery (LCCA), and the internal mammary artery (IMA). The descending aorta (DA) is supplied later through the vertebrobasilar system. Blood flows via the left vertebral artery (LVA) into the left subclavian artery (LSA) and into the descending aorta.*

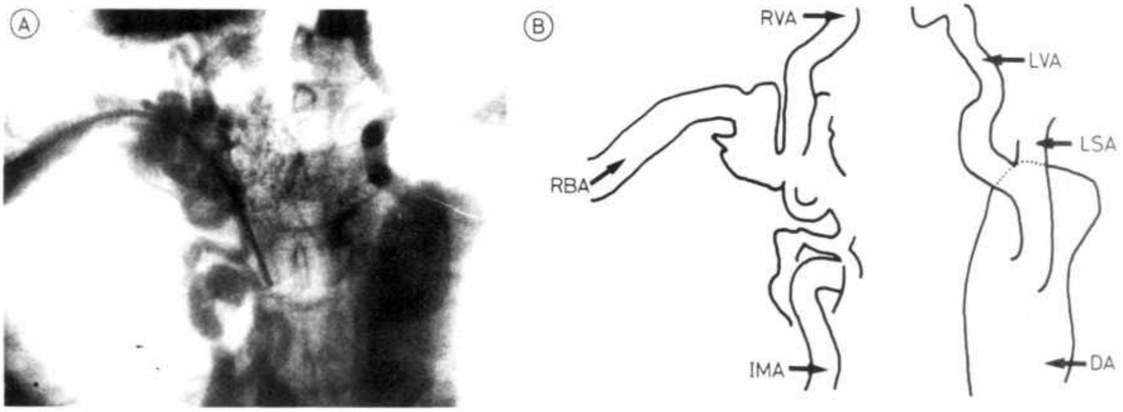

Fig. 2 *(A) A late phase picture of the thoracic arteriogram in the right anterior oblique position. The internal mammary artery is much enlarged and tortuous. The descending thoracic aorta is now visualised. The right and left vertebral arteries are seen with dense opacification of the left vertebral artery. (B) Diagrammatic representation of Fig. 2A. RBA, right brachial artery; RVA, right vertebral artery; LVA, left vertebral artery; LSA, left subclavian artery; DA, descending thoracic aorta; IMA, internal mammary artery.*

mmHg was measured in the ascending aorta and a mean pressure of 70 mmHg in the descending aorta. Both femoral pulses and the left radial pulse were palpable and of good volume. Twenty-four hours after operation simultaneous pressure measurements were made in the right brachial artery and right femoral artery. Systolic pressure in the right brachial artery was 120 mmHg and in the femoral artery 108 mmHg.

On discharge the right arm blood pressure was 130/90 mmHg. Nine months after operation the patient was well but has subsequently left the country and has not been restudied radiologically.

Discussion

Atresia of the aortic arch is a rare malformation and has been reported mainly in association with other cardiac anomalies such as persistent ductus arteriosus and ventricular septal defect. The anomaly is different anatomically from interruption of the aortic arch,

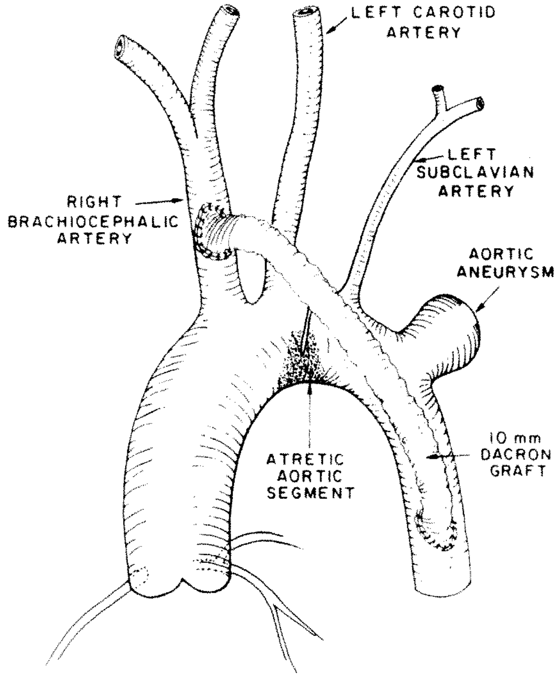

Fig. 3 *Pathological anatomical findings in our patient as seen during operation and the operative treatment. The atretic segment was found between the left common carotid artery and the small left subclavian artery.*

although haemodynamically similar. Whereas in interruption of the aortic arch part of the arch is absent completely, with varying distance between the two ends of the aorta, in atresia of the aortic arch the segment is short, externally narrow, and the lumen not patent. Only one previous case of aortic atresia without additional cardiac anomalies has been reported[6] while others were aortic arch interruptions[1-5 7 8] (Table).

Interruption of the aortic arch was first described in the eighteenth century by Steidele.[10] The currently adopted classification[11] divides the lesion into three types according to the site of interruption: A, interruption distal to the left subclavian artery; B, interruption between the left carotid and left subclavian arteries; C, interruption proximal to the origin of the left carotid artery.

The classification has also been used in atresia of the arch.[12]

In a series of 184 cases of aortic interruption,[13] 42% of the known and classifiable cases (70 of 165) were of type A, 53% of type B, and 4% type C. Almost all cases had associated anomalies: persistent ductus, ventricular septal defects, aorticopulmonary window, bicuspid aortic valve, and muscular subaortic stenosis. When associated with other cardiac malformation, the anomaly carries a 76% mortality within the first month of life,[14] the usual cause of death being early congestive heart failure and/or pulmonary complications. Interruption of the aortic arch with no other cardiac anomalies was thought to be incompatible with life[14] until Pillsbury and associates[2] reported, in 1964, a case in a 16-year-old girl who was operated on successfully. Our case is, to our knowledge, the oldest patient diagnosed and operated on, and is a case of isolated atresia of aortic arch, type B.

It is interesting that all but two reported patients with isolated aortic arch atresia carried their pathology far into adult life, in contrast to the large group of patients with additional intracardiac anomalies who

Table *Clinical data of 11 cases of isolated interruption and atresia of aortic arch*

Author	*Age (yr) and sex*	*Type*	*Blood pressure arms (mmHg)*		*Rib notching*	*Surgical approach*	*Operation*
			Right	*Left*			
Evans[1]	32 M	A (interrupted)	—	—	—	No surgery	
Pillsbury *et al.*[2]	16 F	C (interrupted)	140/100	—	Right side	Left thoracotomy	Bypass graft c̄ 10 mm Dacron tube
Asano *et al.*[3]	12 F	B (interrupted)	210/70	120/60	Right 9th rib	Left lateral thoracotomy, median sternotomy	Bypass graft c̄ 12 mm Dacron tube
Zetterqvist[4]	8 M	B (interrupted)	—	—	No notching	Unknown	Direct anastomosis between ascending and descending aorta
Morgan *et al.*[5]	19 M	B (interrupted)	95/70	95/70	No notching	Left thoracotomy	Bypass graft c̄ 10 mm Dacron tube
Le Page *et al.*[6]	56 M	A (atresia)	184/100	174/90	Right side	Unknown	Direct anastomosis
Kauff *et al.*[7] Case 1	36 M	B (interrupted)	180/120	140/110	Bilateral notching	Left thoracotomy	Direct anastomosis
Kauff *et al.*[7] Case 2	49 M	A (interrupted)	120/90	210/95	Bilateral notching	Left thoracotomy	Bypass c̄ Dacron tube graft
Judez *et al.*[8]	18 F	B (interrupted)	—	—	No notching	No surgery	
Sharratt *et al.*[9]	15 M	B (interrupted)	220/90	—	Right side	Median sternotomy and left thoracotomy	Bypass graft c̄ 20 mm Dacron tube
Present case	65 M	B (atresia)	145/120	—	Right side	Left thoracotomy	Bypass graft c̄ 10 mm Dacron tube

succumbed early in childhood.[14] Symptoms resembled those of long-standing systemic hypertension or aortic coarctation: headaches, fainting spells, visual disturbances, dysphasia, memory loss, dyspnoea, and leg pains on walking. Central nervous system symptoms seen in cases with interruption of types B and C are probably the result of vertebral steal.[4 9] Retrograde flow from the left vertebral and carotid arteries to the descending aorta was present in our patient and carotid arteriograms showed filling of the vertebrobasilar system from an injection into the right carotid artery (Fig. 2A and B). Reconstitution of blood flow to the descending aorta was achieved at operation, either by direct anastomosis (cases 4, 7, 9) or by use of a synthetic tube graft, depending on the anatomical distance between the two end pouches of the ascending and descending aorta and the feasibility of bringing them together. Operation was successful in all patients included in this review. Surgical treatment of the anomaly is relatively simple and produces distinct improvement in both neurological and cardiovascular status.

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Requests for reprints to Dr Simcha Milo, Department of Thoracic and Cardiovascular Surgery, The Chaim Sheba Medical Center, Tel-Hashomer, Israel.

Br Heart J 1982; **47**: 298–300

Echocardiographic diagnosis of isolated pulmonary valve endocarditis

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From the Cardiology Department, Ospedale Civile Verona, Italy

SUMMARY A patient is described in whom diagnosis of isolated pulmonary valve endocarditis was made by M-mode and two dimensional echocardiography. Angiography confirmed the presence of vegetations on the pulmonary valve. At cardiac surgery a quadricuspid, non-stenotic valve with ruptured medial leaflet covered by necrotic vegetations and a small ventricular septal defect were found.

Echocardiography is known to be useful in diagnosing valvular endocarditis[1 2] of the mitral and aortic valves but only two cases of pulmonary valve endocarditis have been previously diagnosed in this way. We report another.

Case report

A 46-year-old man, known to have an undiagnosed asymptomatic congenital heart defect, had a high temperature in November 1979. He was treated with antibiotics which were at first effective but pyrexia reappeared two weeks later. Cephalosporin was given intravenously for 10 days, but the patient became very weak, and haemorrhagic purpura appeared on the legs; evening pyrexia persisted. Finally, in May 1980, he was admitted to this hospital; bacterial endocarditis was suspected and penicillin started.

At physical examination the patient appeared very ill and febrile, with gross hepatosplenomegaly. A grade 4/6 harsh pansystolic murmur was heard in the second and the third left intercostal space followed by a grade 1/6 diastolic murmur. The second heart sound was almost inaudible on the pulmonary area.

The electrocardiogram and chest *x*-ray film appeared to be within normal limits. The M-mode echocardiogram (Fig. 1) showed multiple dense echoes on the posterior leaflet of the pulmonary valve, which showed abnormal movement. The two dimensional echocardiographic examination (30° sector scan) (Fig. 2) showed large polypoid vegetations freely moving with the cardiac cycle between the outflow tract of the right ventricle and the main pulmonary artery. Repeated blood cultures grew *Staphylococcus cutis*.

Treatment with cefuroxime led to a brief remission of fever with apparent clinical improvement but high fever reappeared after 10 days despite continuous treatment and finally the patient developed a left lower lobe infarction with pleural effusion. As he was so ill, cardiac catheterisation and angiocardiography, previously planned, were abandoned and cardiac surgery was performed on the evidence of the echocardiographic diagnosis on 5 June. The pulmonary artery was incised transversely above the level of the valve. A quadricuspid non-stenotic valve was seen; the medial leaflet was ruptured and covered by an overgrowth of necrotic tissue (Fig. 3); a small ventricular septal defect was found just below the pulmonary valve which was excised. A biological prosthesis was inserted, and the ventricular septal defect sutured with four stitches on Teflon pledgets.

Culture of the valve grew *Staphylococcus cutis*.

Comment

Right sided endocarditis, particularly of the pulmonary valve, is rare. While the tricuspid valve is frequently infected in narcotic addicts, pulmonary valve involvement was described in only two of 127 such cases[3-6] and never as an isolated finding.

Isolated pulmonary valvar infection is indeed exceptional. Of 149 cases of infective endocarditis in children reported by Johnson *et al.*,[7] there was only one case, in a patient with severe pulmonary stenosis.

Only two cases of pulmonary valve endocarditis diagnosed by means of echocardiography have been reported. The first, described by Kramer *et al.* in 1977,[8] occurred in a young heroin addict with multivalvular involvement. The second was reported in

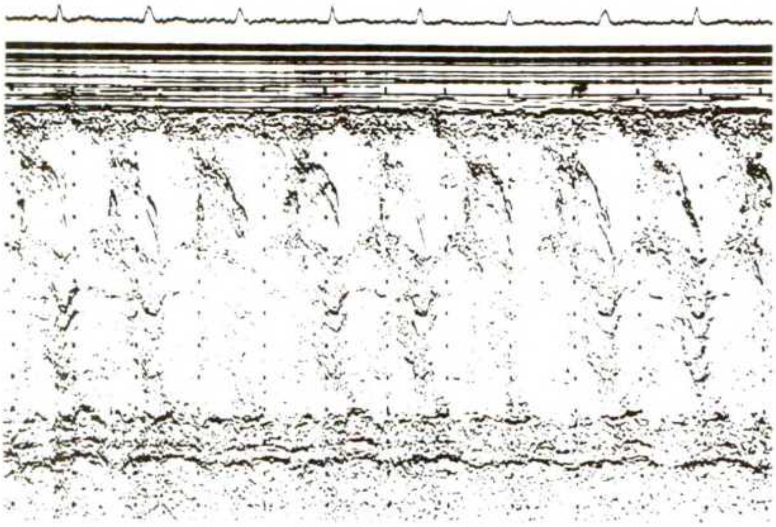

Fig. 1 *M-mode echocardiogram showing multiple, dense, shaggy echoes on the pulmonary valve.*

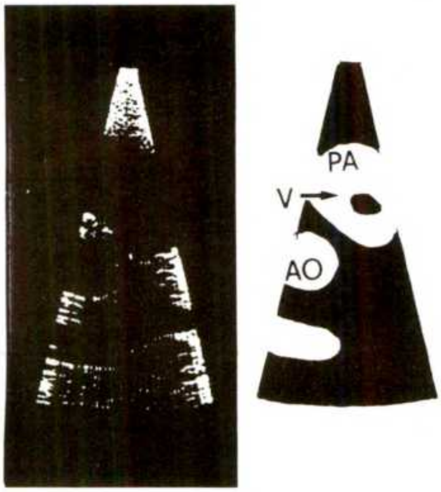

Fig. 2 *Cross-sectional echocardiogram in the short axis view, illustrating a large mass (V) on the pulmonary valve consistent with a vegetation. PA, pulmonary artery; AO, aorta; V, vegetation.*

1979 by Dzindzio *et al.*[9]; the organism was the gonococcus which was though to have a particular affinity for the pulmonary valve.

Our patient was not a narcotic addict, and did not have a gonococcal infection or pulmonary valve stenosis. Echocardiography was diagnostic, indicating which valve had vegetations. M-mode echocardiography showed these as shaggy, irregular large echoes on the medial leaflet of the pulmonary valve, and the two dimensional technique gave precise information about their size and mobility.

On the basis of these findings it was thought that endocarditis had occurred on a mild congenital pulmonary valve stenosis. At surgery, however, a small ventricular septal defect was found with a malformed but non-stenotic pulmonary valve. We suggest that

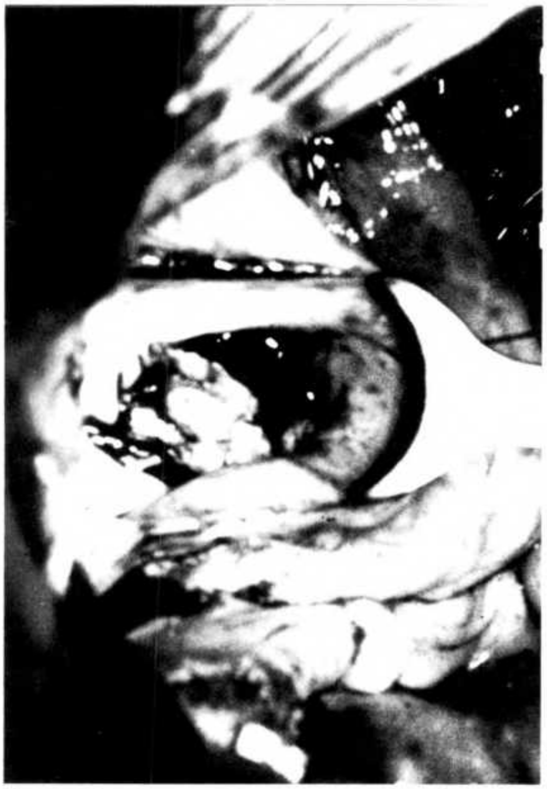

Fig. 3 *The pulmonary valve at surgery seen from above: on the anteromedial aspect there is a large polypoid endocarditic vegetation.*

the ventricular septal defect may have produced a jet lesion on the pulmonary valve that predisposed to infection.

The clinical course of this patient, with the poor response to medical treatment and the complication of pulmonary embolisation, made surgery the best form of treatment for this particular case.

The authors wish to acknowledge the help in the study and treatment of this case given by Drs R Albiero (surgical intervention) and C Buonanno (angiographic study).

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Br Heart J 1982; **47**: 301–3

Rapid disappearance of left ventricular mass (presumed thrombus) in a patient with cardiomyopathy

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SUMMARY A man aged 41 years with a clinical diagnosis of cardiomyopathy and hepatic insufficiency was found, on angiocardiography, to have a mass, presumably a thrombus, within the left ventricle. A second angiocardiogram performed five days later showed that the thrombus had disappeared. The mechanism invoked was more probably an increase of spontaneous fibrinolysis as described in cirrhotic patients, perhaps helped by heparin, rather than ejection of the mass from the ventricle with silent embolisation somewhere in the systemic circulation.

The detection of a left ventricular mass in vivo may be made by angiocardiography. Two dimensional echocardiography is, however, the best and the most sensitive technique. A left ventricular mass is usually a thrombus but occasionally a tumour. We report a patient with congestive cardiomyopathy in whom a left ventricular mass apparently disappeared within five days of its detection by angiocardiography.

Case report

A 41-year-old man, a labourer, was admitted to hospital on 24 August 1979, because of congestive heart failure. There was a past history of heavy alcohol ingestion and laboratory data showed hepatic insufficiency (Table 1). The blood pressure was 110/70 mmHg, pulse regular at 116/min, and temperature normal. The erythrocyte sedimentation rate was 3 mm in one hour. There was venous distension and oedema of both legs. Basal râles were heard in the chest. There was a faint systolic murmur 1/6 at the apex. The heart was enlarged on chest radiography (cardiothoracic ratio 0·62). The electrocardiogram showed sinus tachycardia with left ventricular hypertrophy and left bundle-block branch. An M-mode echocardiogram recorded at the fourth intercostal space at the left sternal edge showed dilatation of the left ventricular cavity with an end-diastolic dimension of 6 cm and a very hypoactive interventricular septum. The patient was regarded as having congestive cardiomyopathy. He was given digitalis and diuretics and the result was good.

Cardiac catheterisation on 31 August 1979 (Table 2) showed an increase of both right and left ventricular end-diastolic pressures. The cardiac index was 2·4 l/min per m², left ventricular end-diastolic volume was 182 ml/m², and the ejection fraction was 0·21.

Selective left ventricular cineangiography in the right anterior oblique projection disclosed dilatation and considerable hypokinesia of the left ventricle. In addition, angiography showed a mobile left ventricular filling defect at the apex during diastole moving

Table 2 *Cardiac catheterisation data*

	Pressure (mmHg) Systolic/diastolic	*Mean*
Right atrium	17/9	13
Right ventricle	55/16	—
Main pulmonary artery	55/32	40
Wedge pressure	38/23	30
Left ventricle	120/35	—
Aorta	120/90	100

Table 1 *Laboratory data*

Albumin (g/l)	*Alkaline phosphatase*	*AST* (U/ml)*	*ALT* (U/ml)*	*γGT* (U/ml)*	*BSP* retention (%)*	*Prothrombin time (%)*	*Total cholesterol (mmol/l)†*	*Bilirubin (μmol/l)†*
36	12	41	62	74	100	60	2·7	6·84

*Abbreviations: AST, serum aspartate aminotransferase; ALT, serum alanine aminotransferase; γGT, gamma glutamyl transferase (normal value <40); BSP, bromsulphophthalein.
†Conversion from SI units to traditional units: cholesterol 1 mmol/l ≈ 38·6 mg/100 ml; bilirubin 1μmol/l ≈ 0·058 mg/100 ml.

toward the aortic valve in systole (Fig. 1). The size of the defect was 2·5 × 1·5 cm. The patient was considered to have a left ventricular thrombus rather than a left ventricular tumour. Heparin was given intravenously at the rate of 40 mg (4000 IU) every three hours and surgical treatment was planned. Before this, however, a further cineangiogram was taken on 5 September 1979. It was surprising to see that the left ventricular filling defect had disappeared (Fig. 2). The patient had not shown peripheral or cerebral emboli. Selective coronary arteriography was normal. The patient was discharged home on 9 September 1979. He was seen four, eight, and 12 months later and was reasonably well, taking anticoagulant therapy, digitalis, and diuretics.

Discussion

The left ventricular mass was considered to be a thrombus particularly because the underlying disease was a cardiomyopathy. Left ventricular thrombi occur frequently in cardiomyopathies, with an incidence of 25 to 50% of necropsied patients, according to Perrin *et al.*[1] and Reeder *et al.*[2]

The disappearance of this mass, recognised five days after anticoagulant treatment, can be explained

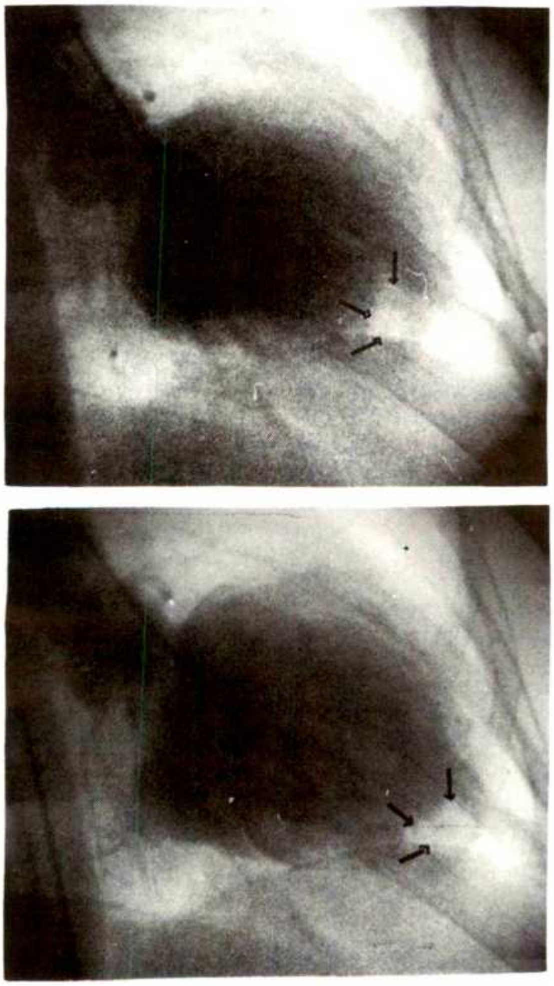

Fig. 1 *First cineangiography performed on 31 August 1979. Left ventriculogram in the right anterior oblique projection, in systole (top) and diastole (bottom). Note the filling defect at the apex of left ventricle.*

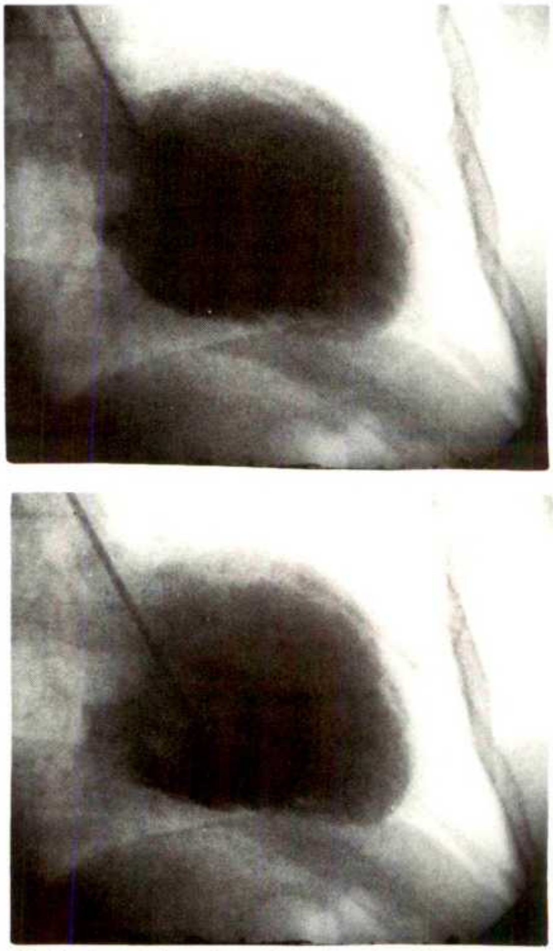

Fig. 2 *Second cineangiography performed on 5 September 1979. Left ventriculogram in systole (top) and diastole (bottom). Note the disappearance of the filling defect. The similar appearance of the left ventricular cavity in systole and diastole indicates severe generalised hypokinesia, presumably a result of cardiomyopathy.*

in one of two ways. The first is expulsion from the ventricle to produce silent embolisation somewhere in the systemic circulation. Miller *et al.*[3] have reported several cases of silent emboli, especially involving the spleen or kidneys in acute and in healed myocardial infarction. The second explanation which seems the more probable is lysis of the thrombus. According to Fletcher *et al.*[4] and to Pises *et al.*,[5] disappearance of the thrombus could be explained by increased spontaneous fibrinolysis. Our patient had severe hepatic insufficiency and these authors[4 5] showed abnormally active fibrinolysis in cirrhotic patients, probably the result of failure of hepatic clearance mechanisms for plasminogen activator.

Other cases of disappearance of left ventricular thrombi have been previously reported.[6 7] Mikell *et al.*[6] have followed 15 patients, eight with chronic cardiomyopathy and seven with recent myocardial infarction, in whom left ventricular thrombi were discovered. They performed serial two dimensional echocardiograms, 33 to 240 days after initial examination. In the nine patients who received anticoagulation for at least 30 days, left ventricular thrombi resolved in five cases, decreased in size in two cases, and remained unchanged in two cases. No patient had clinically apparent emboli. In the six patients who did not receive anticoagulant treatment, the left ventricular thrombi remained apparently unchanged in five cases, and the size of the thrombus decreased in one case; two patients had emboli. Meltzer *et al.*,[7] also using serial two dimensional echocardiograms, found a reduction in size of left ventricular thrombi at 10-month follow-up in two patients, and in one of them the mass had disappeared after 19 months.

According to these reports and in view of our own case we suggest that when a left ventricular mass is discovered in patients with cardiomyopathy, anticoagulant treatment should be given and surgical treatment may be delayed. Serial two dimensional echocardiograms are advised to follow the size of the intraventricular mass. If echocardiography does not show the mass, then a second angiocardiogram may be considered before surgical intervention is advised.

The authors wish to thank Dr R G Grainger of Sheffield for his help.

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Notices

Br Heart J 1982; **47**: 304

Eighth Asian-Pacific Congress of Cardiology

The Second Asian-Pacific Symposium on Cardiac Pacing will be held in Manila on 23 to 25 November 1983 preceding the 8th Asian-Pacific Congress of Cardiology to be held in Taiwan on 27 November to 3 December 1983. For further information write to: Agripino D Reloza MD, Secretary-General, Second Asian-Pacific Symposium on Cardiac Pacing, Philippine Heart Association, c/o Philippine Heart Center for Asia, East Avenue, Quezon City, Philippines.

Year of tropical cardiology 1982

In view of its interest in the problems of cardiovascular diseases in the tropical and developing areas of the world, the International Society and Federation of Cardiology has designated 1982 as the Year of Tropical Cardiology. This project has the support and collaboration of the World Health Organisation and a number of meetings and seminars have been organised to discuss the problems of cardiovascular diseases in the developing nations and in the tropics.

Dr E G J Olsen, Chairman of the ISFC Scientific Council on Cardiomyopathies, is in charge of the arrangements and any inquiries, including those about meetings already planned, should be addressed to him: Dr Eckhardt G J Olsen, Department of Histopathology, National Heart Hospital, Westmoreland Street, London W1M 8BA.

Subacute bacterial endocarditis

A survey is currently being carried out by the British Cardiac Society and the Medical Services Study Group of the Royal College of Physicians. Though improvement of dental prophylaxis is one objective, the survey is already yielding other valuable information. It is hoped that proformas will be received in respect of a high proportion of patients with subacute bacterial endocarditis in the British Isles seen during 1981 and 1982 and readers are asked to arrange for them to be submitted in respect of any cases that come to their notice. Proformas can be obtained from Sir Cyril Clarke, Medical Services Study Group, King's Fund Centre, 126 Albert Street, London NW1 7NF (tel. 01-267 6111, ext. 263) to whom they should be returned.

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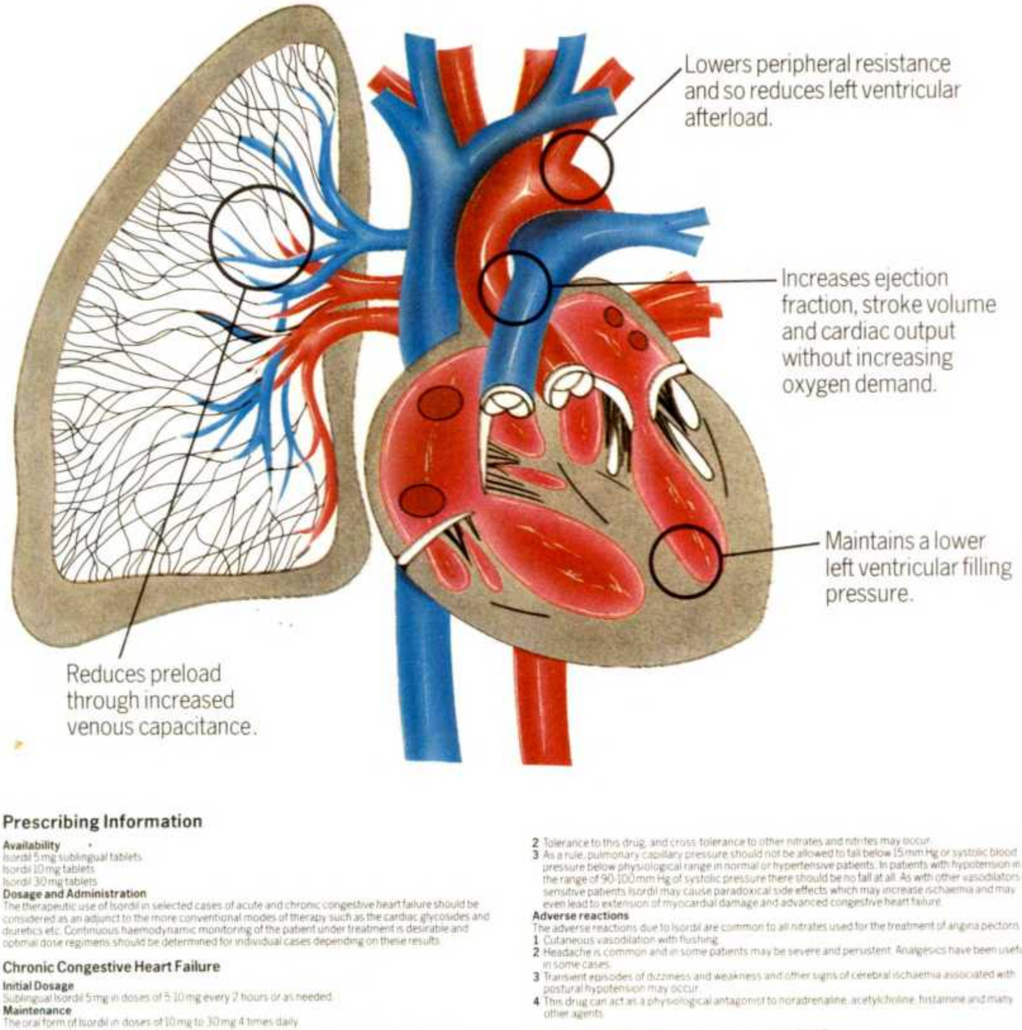

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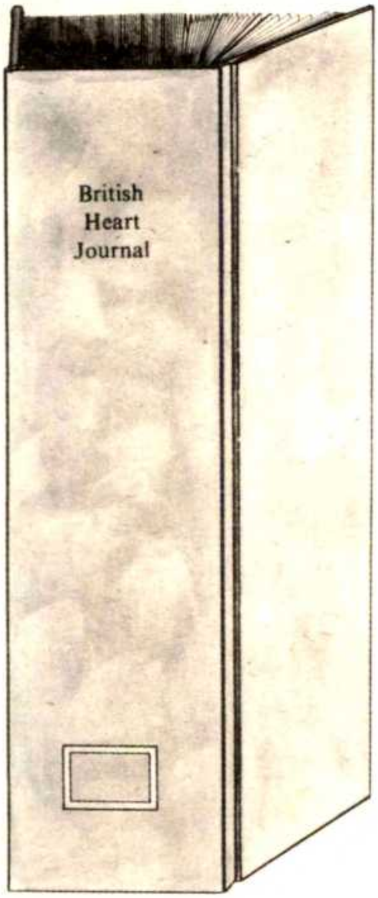

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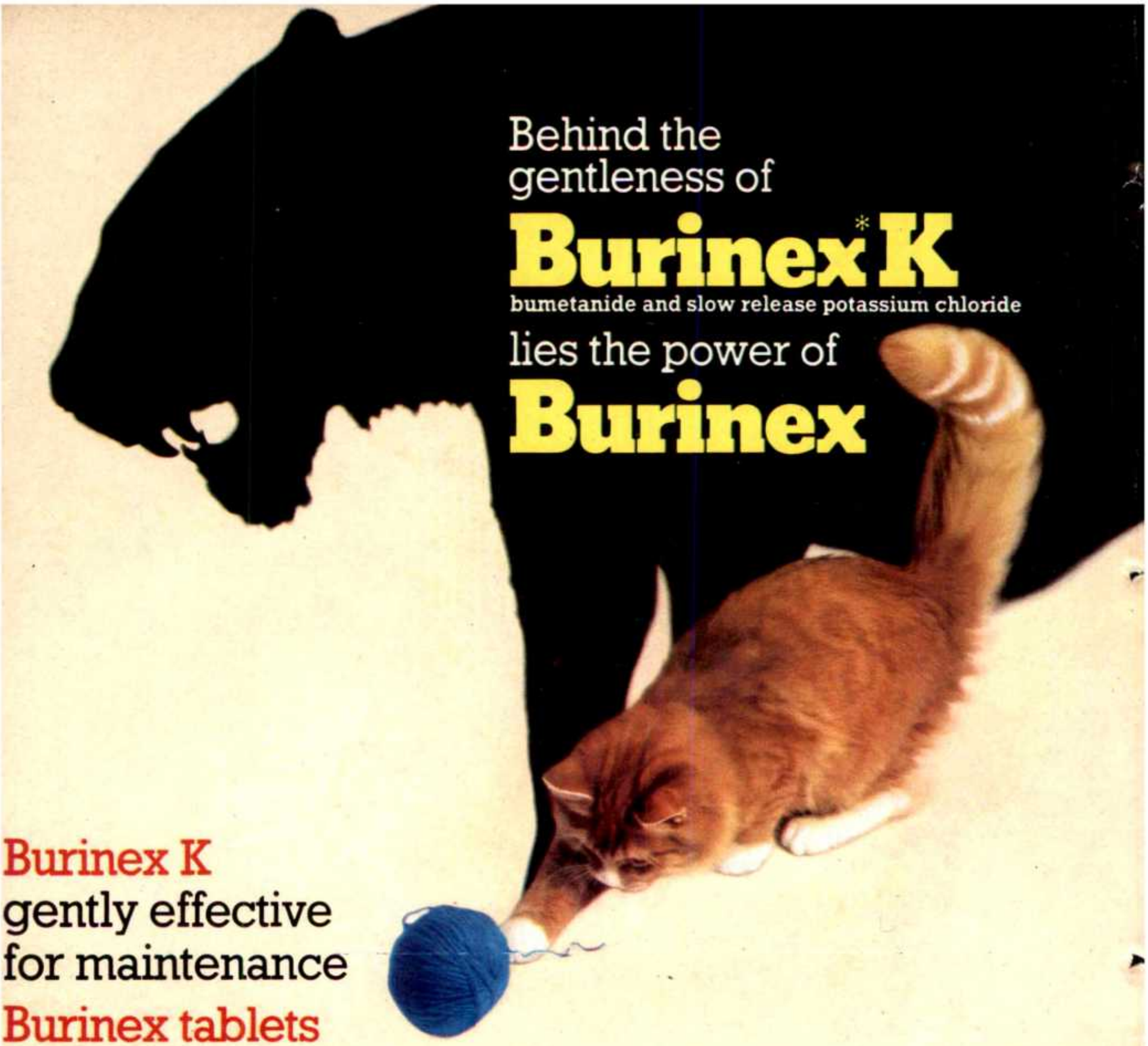

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British Heart Journal

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(1) *Standard journal article*—(List all authors when six or less; when seven or more, list only first three and add *et al.):*
  Walmsley R. Anatomy of left ventricular outflow tract. *Br Heart J* 1979; **41**: 263–7.

(2) *Books and other monographs:*
  Macartney FJ, Partridge JB, Shinebourne EA, Tynan MJ, Anderson RH. Identification of atrial situs. In: Anderson RH, Shinebourne EA, eds. *Paediatric cardiology 1977*. Edinburgh, London: Churchill Livingstone, 1978: 16-26.

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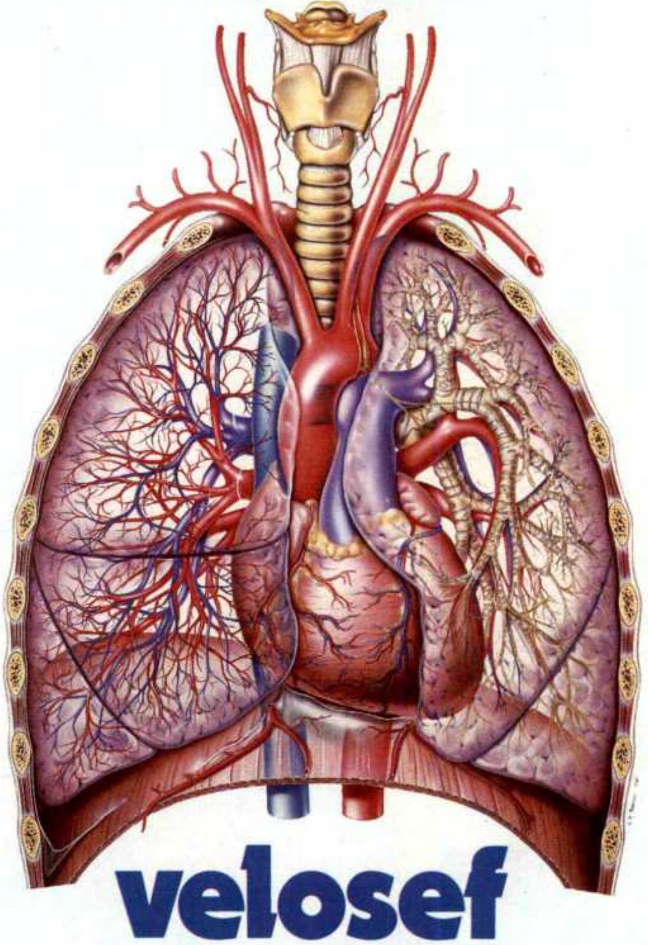

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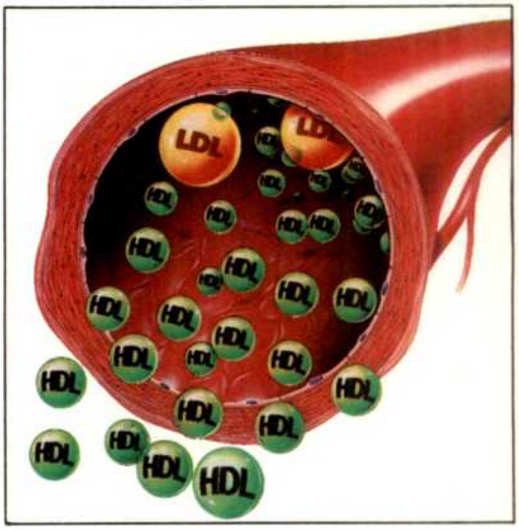

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1. *JAMA*, **62** (1977) 707
2. Manufacturers' Literature
3. Lipoproteins and Coronary Heart Disease, Witzstrock Publishing House, New York (1980) 185-188
4. *Ibid:* 192-195
5. *Munch. med. Wschr.* **122, 5** (1980) 165-168
6. Diet and Drugs in Atherosclerosis, eds. G. Noseda, B. Lewis, R. Paoletti, Raven Press, New York (1980) 137-142

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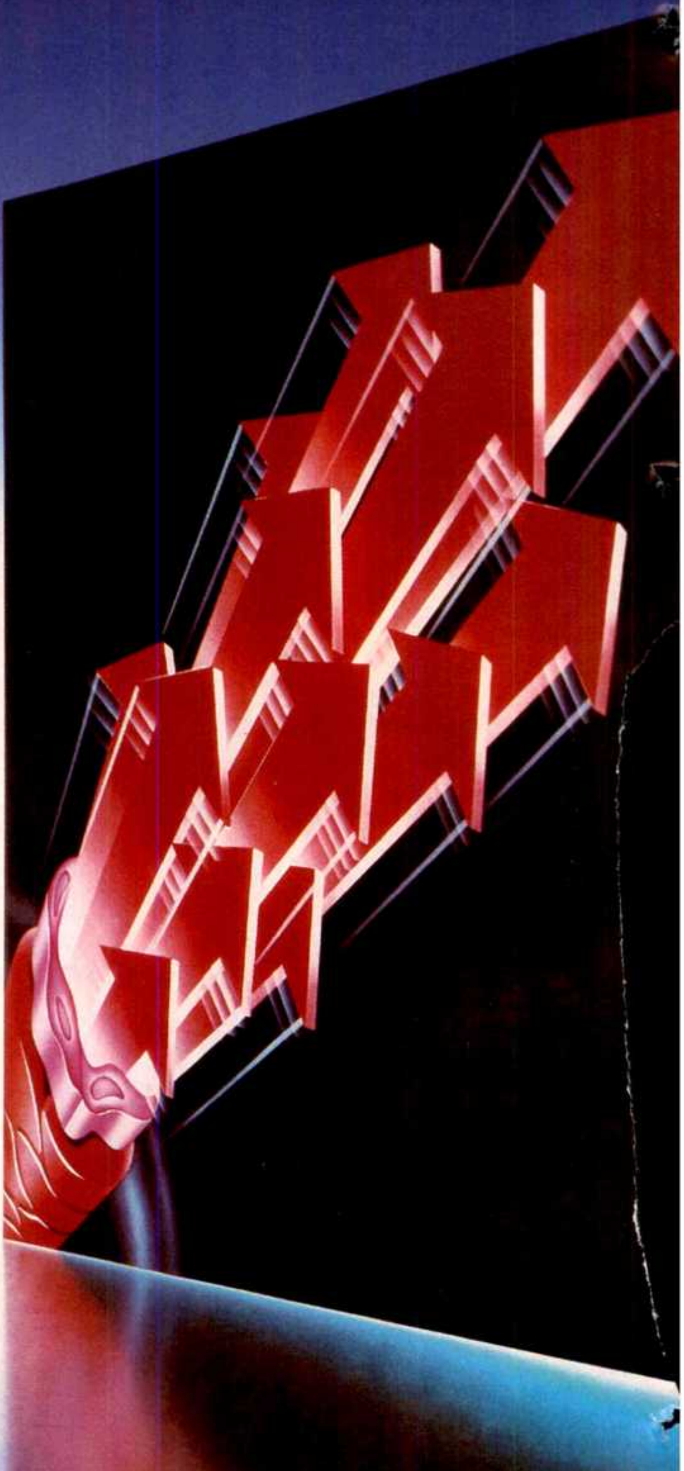

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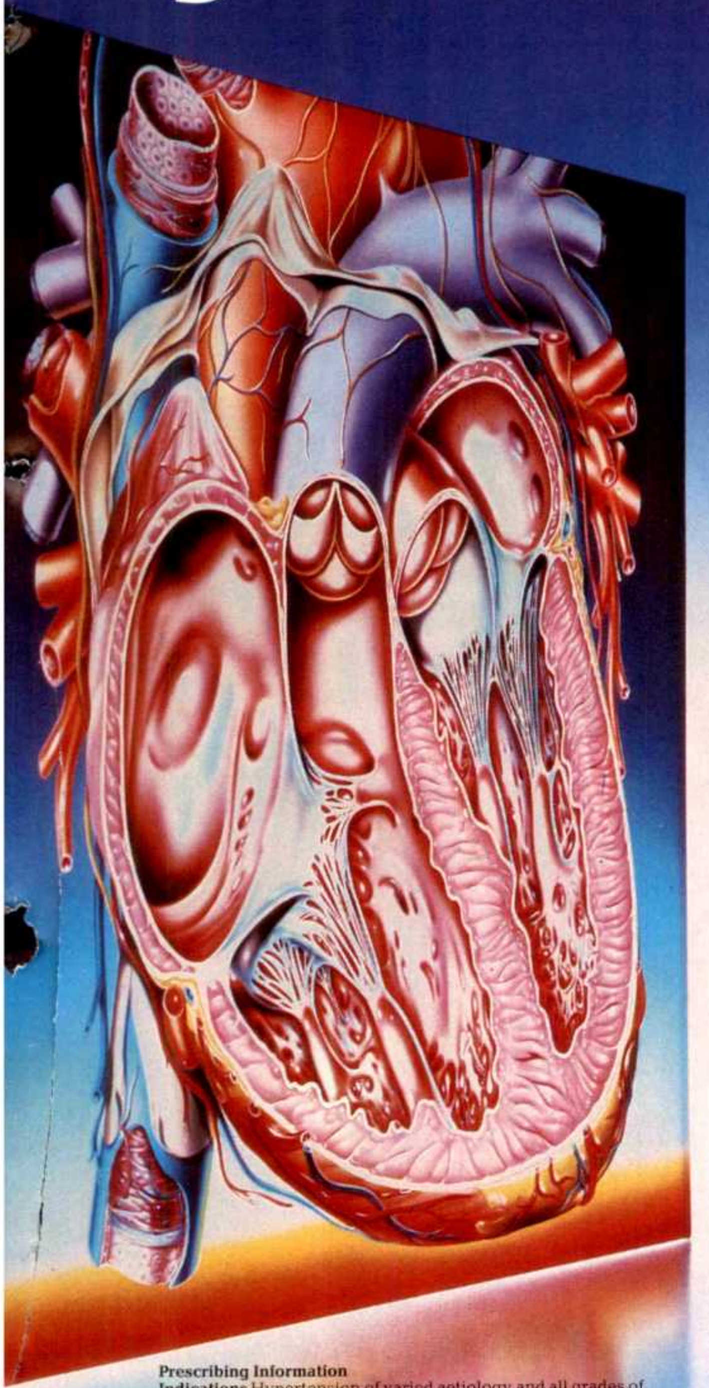

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1. Turner, A.S., et al. Med. J. Aust., Spec., Suppl., (1977), **2**, 33-37.
2. Fauchald, P., et al. Excerpta Medica International Symposium, Vienna, November (1978), 85-93.
3. Bossi, M, et al. Excerpta Medica Symposium, Tokyo (1978), 107.
4. Hutton, I, et al. European Prazosin Symposium (1978), 138.

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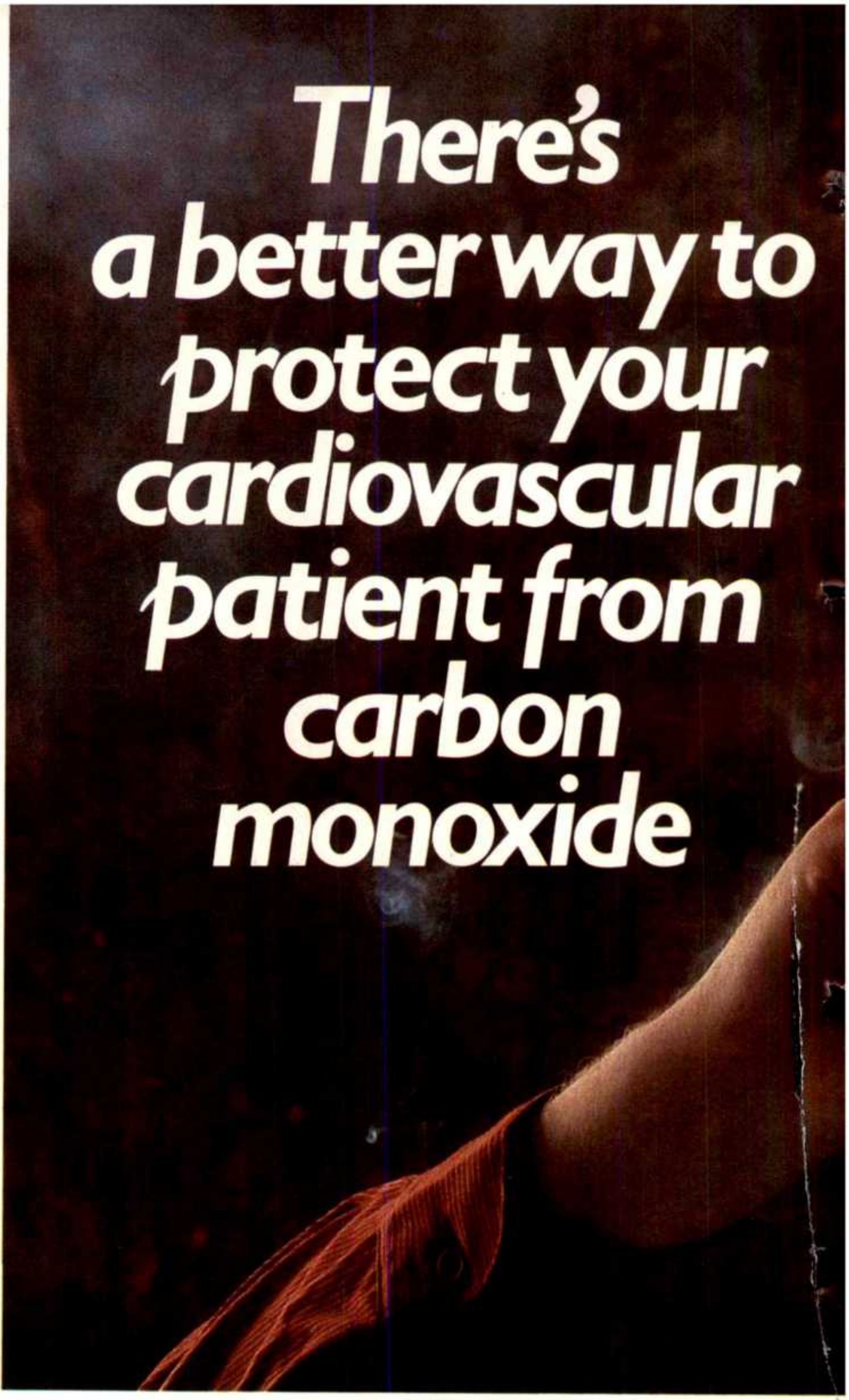

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References: *1. Aronow WS. Effect of Cigarette Smoking and of Carbon Monoxide on Coronary Heart Disease. Chest 1976; 70: 54-157. 2. Tibblin G, Wilhelmsen L, Werkö L. Risk Factors for Myocardial Infarction and Death Due to Ischemic Heart Disease and Other Causes. American Journal of Cardiology 1975; 35: 514-522. 3. Russell MAH, Wilson C, Taylor C, Baker CD. Brit med J 1979; 2: 231-235. 4. Raw M, Jarvis MJ, Feyerabend C, Russell MAH. Brit med J 1980; 281: 481-482.*

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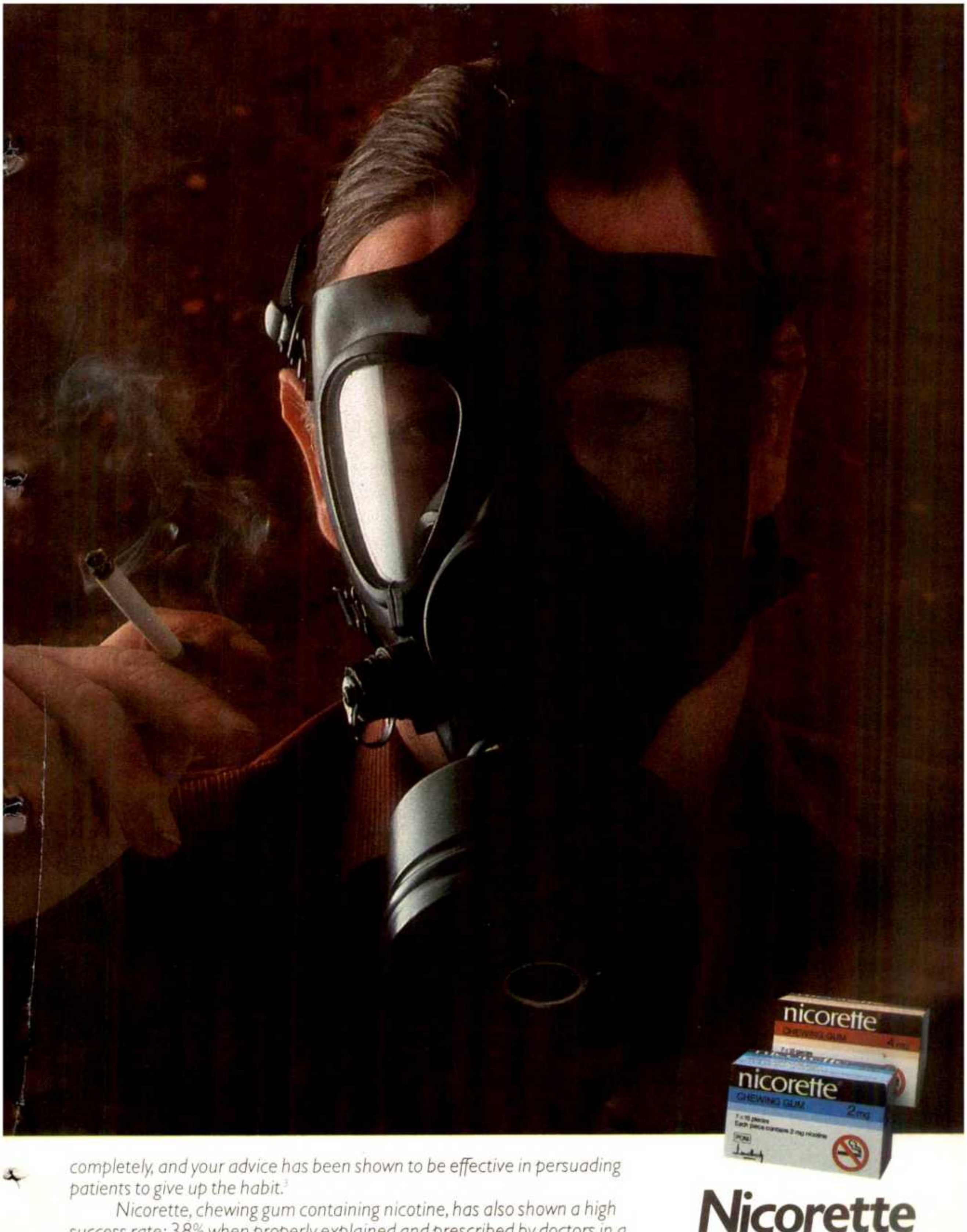

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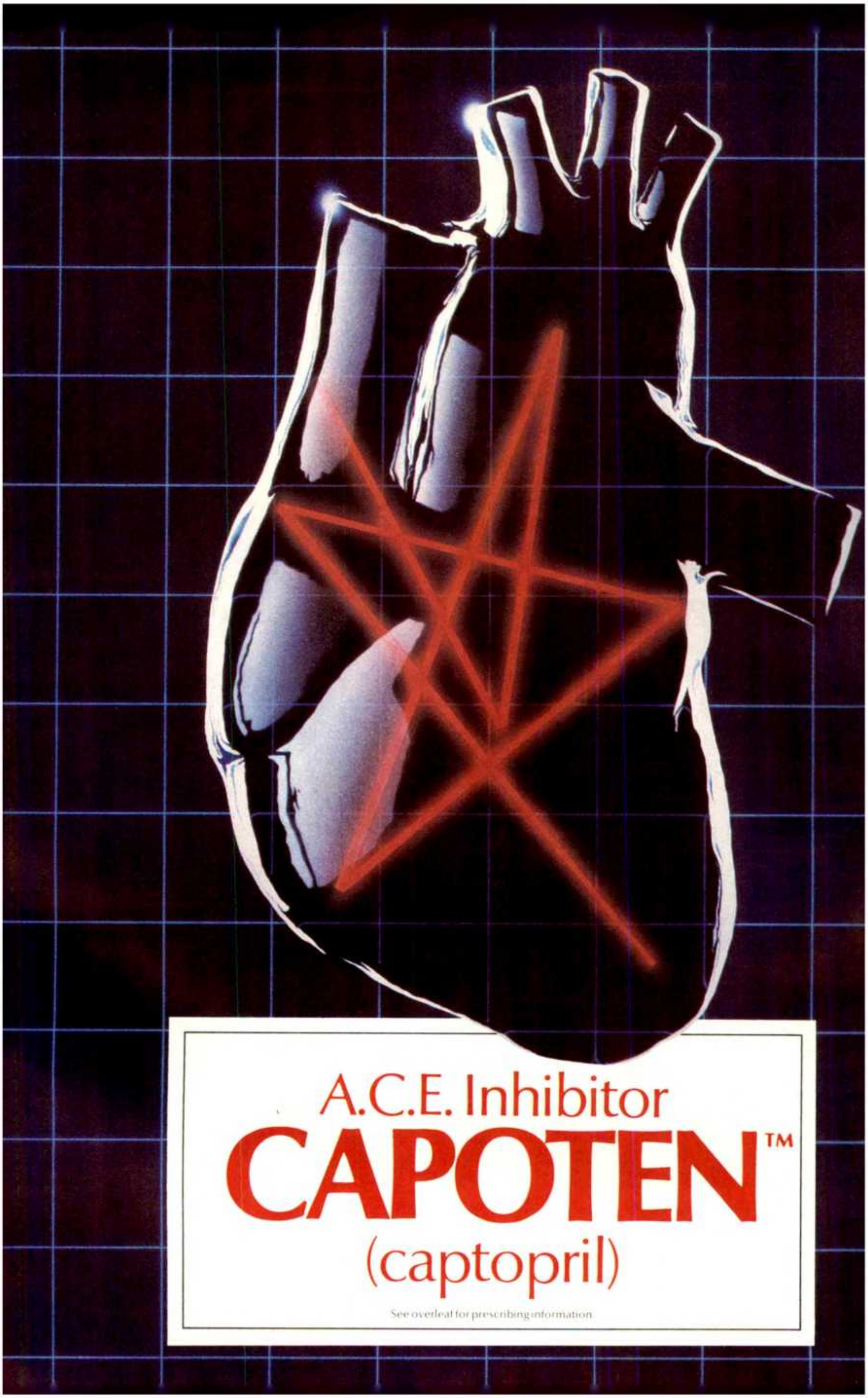

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Sustained effectiveness

Capoten effectively breaks the vicious circle in heart failure by reducing preload and afterload without invoking compensatory mechanisms, such as increased heart rate and fluid retention. Long term effectiveness is thus sustained on Capoten therapy.[5,6]

A.C.E.* Inhibitor

CAPOTEN™

(captopril)

*Angiotensin converting enzyme

Improves cardiac performance without increasing heart rate

In patients with resistant heart failure Capoten..." significantly raised cardiac output and reduced arterial, pulmonary-wedge, and pulmonary-artery pressures which correlated closely with concomitant alterations in the activity of the renin-angiotensin system."[7]

Improves the patients' quality of life

By reducing preload, Capoten helps to relieve pulmonary congestion and dyspnoea. By reducing afterload, Capoten increases cardiac output and stroke index.

"Side effects of the drug (Capoten) have not been observed and most patients have objective and subjective evidence of improvement."[8]

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"Captopril is a major advance in the treatment of resistant heart failure..."

(Lancet 1981; 1: 71-74)

References

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Prescribing information

CAPOTEN™ TABLETS Capoten tablets each contain 25 mg, 50 mg or 100 mg captopril. **USES** Capoten (captopril) in hypertension appears to lower blood pressure primarily by renin-angiotensin-aldosterone inhibition. Usage in hypertensive crises should be avoided. It has also been shown to be of benefit in the management of severe, treatment-refractory congestive heart failure. **Indications Hypertension** The treatment of severe hypertension where standard therapy has failed. **Congestive Heart Failure** Capoten is indicated for the treatment of severe, treatment-refractory congestive heart failure. The drug should be used together with diuretics and digitalis, but only after these agents have failed to produce a satisfactory response. **DOSAGE AND ADMINISTRATION** Capoten should be taken one hour before meals. **Adults Hypertension** The usual dose range of Capoten is 25-150 mg t.i.d. The maximum recommended daily dose is 450 mg. The initial daily dose of Capoten is 25 t.i.d. which should be increased to 50 mg t.i.d. if a satisfactory reduction of blood pressure has not been achieved in two weeks. If a satisfactory response has not been achieved after a further two weeks a modest dose of a thiazide diuretic (hydrochlorothiazide) or in patients with impaired renal function a loop diuretic (frusemide) should be added. The diuretic should be increased until a satisfactory response is obtained or its maximal dose is reached. Should Capoten 50 mg t.i.d. together with the diuretic fail to give a satisfactory reduction in blood pressure, then Capoten should be increased to 100 mg t.i.d., and then, if necessary, 150 mg t.i.d. For patients with accelerated or malignant hypertension, who are unresponsive to conventional therapy, it may be necessary to increase the daily dose of Capoten every 24 hours, until a satisfactory blood pressure response is obtained or the maximum dose of Capoten is reached. When Capoten is used alone, concomitant sodium restriction may be advantageous. Capoten may be used in conjunction with other antihypertensive agents, particularly thiazide diuretics and beta-blockers. **Congestive Heart Failure**. The usual starting daily dose is 25 mg t.i.d. and the usual effective dose range is between 25 and 150 mg t.i.d. After a dose of 50 mg t.i.d. is reached, further increases in dose should be delayed, where possible, for several weeks to determine if a satisfactory response occurs. Capoten should be used in conjunction with the highest usual doses of diuretic and with digitalis. Capoten therapy must be started in the hospital (see Warnings). A maximum daily dose of 450 mg of Capoten should not be exceeded. **Patients with Renal Impairment** About 75% of a given daily dose of Capoten is usually excreted in the urine; Capoten retention occurs in the presence of impaired renal function. The dosage interval should be increased as follows when creatinine clearance is below 75 ml/min/1.73 m^2:

Creatinine Clearance (ml/min 1.73 m^2)	Dosage Interval (Hours)
>75	8
75-35	12-24
34-20	24-48
19-8	48-72
7-5	72-108 (3 to 4.5 days)

When concomitant diuretic therapy is required, a loop diuretic (e.g. frusemide) is preferable to a thiazide diuretic.

Children Safety and effectiveness in children have not been established. Starting dose should be 1 mg per Kg bodyweight up to a maximum of 6 mg per Kg bodyweight divided into three doses per day. **CONTRA-INDICATIONS, PRECAUTIONS AND WARNINGS:- Contra-Indications** Previous hypersensitivity to Capoten **Warnings** NEUTROPENIA/AGRANULOCYTOSIS and PROTEINURIA have been reported in patients receiving Capoten. Urinary protein should be checked (dip stick) prior to treatment, monthly for 8 months and periodically thereafter. WBC should be carried out prior to treatment, fortnightly for three months and periodically thereafter. **Hypotension** A precipitous reduction of blood pressure may occasionally occur within the first three hours following the initial dose of Capoten in patients on diuretics, on a low sodium diet or undergoing dialysis. An exaggerated hypotensive effect may also occur with one or two subsequent doses. Medical supervision should be maintained for one hour after the initial dose. This transient hypotensive response is not a contra-indication to further doses which can be given without difficulty once blood pressure has increased after volume expansion. **Hypotension in Patients with Severe Congestive Heart Failure**. These patients, having either normal or low blood pressure, may experience marked falls in blood pressure, which have on rare instances been associated with arrhythmia or conduction defects, after the first few doses of Capoten. Because of the potential fall in blood pressure in these patients, therapy must be started in the hospital. Patients should be followed closely for the first two weeks of treatment and whenever the dose of Capoten and/or diuretic is increased. Patients treated for severe congestive heart failure should be warned to increase their physical activity slowly. **Serum Potassium** Since Capoten decreases aldosterone production, elevation of serum potassium may occur, especially in patients with renal failure. Potassium sparing diuretics or potassium supplements, if needed, should be used with caution, since they may lead to a significant increase in serum potassium. **Changes in Renal Function** Some patients with renal disease, particularly those with renal artery stenosis, have developed increased serum concentration of BUN and serum creatinine after reduction of blood pressure with Capoten, usually along with a diuretic. Capoten dosage reduction and/or discontinuation of diuretic may be required. For some of these patients, it may not be possible to normalise blood pressure and maintain adequate renal perfusion. **Pregnancy** The safety of Capoten in pregnancy has not been established. **Nursing Mothers** Exercise caution. **Surgery/Anaesthesia** In patients undergoing major surgery, or during anaesthesia with agents which produce hypotension, Capoten will block angiotensin II formation secondary to compensatory renin release. This may lead to hypotension which can be corrected by volume expansion. Capoten may cause a false-positive urine test for acetone. **Side Effects** Neutropenia/Agranulocytosis Proteinuria see Warnings. Skin rashes and taste disturbance have been reported. Gastric irritation and abdominal pain may occur. **Other** Paraesthesias of the hands, serum sickness, cough, bronchospasm and lymphadenopathy have been reported. Hypotension – see Warnings. Tachycardia has been observed in a few volume depleted patients. **Overdosage** In the event of overdosage, hypotension would be the most important problem. Volume expansion with an intravenous infusion of normal saline is the treatment of choice for restoring the blood pressure to normal. Capoten is removed by dialysis. **PACKAGE QUANTITIES** in bottles of 100. **Basic NHS Price** 25 mg tablets 100 - £21.40. **PRODUCT LICENCE NUMBERS, NAMES AND ADDRESSES Product Licence Numbers** Capoten tablets 25 mg PL 0034/0193;
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Conduction defects, ventricular arrhythmias, and late death after surgical closure of ventricular septal defect

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SUMMARY One hundred and eighty-seven patients who had surgical closure of a ventricular septal defect between 1958 and 1975 were followed for up to 21 years. There were 17 late sudden deaths of which eight occurred in completely fit patients while nine were already under medical care. In an attempt to elucidate possible risk factors the preoperative and serial postoperative electrocardiograms of all patients were studied. Fifty-one unselected healthy follow-up patients agreed to 24 hour ambulatory monitoring. Progressive exercise testing (Bruce protocol) was carried out on 31 of them and an additional seven patients. There was a significant correlation between recorded ventricular arrhythmias and conduction defects, particularly progressive conduction defects. Transient complete heart block carried a bad prognosis and grade 3–4b ventricular arrhythmias were a major risk factor and recorded in 10 of the 17 patients who died. Long-term postoperative electrocardiographic follow-up is recommended and 24 hour ambulatory monitoring and exercise testing complement the findings of the resting electrocardiogram. The long-term treatment of survivors found to have ventricular arrhythmias must be considered.

With an incidence of about two in 1000 live births, ventricular septal defect is one of commonest congenital abnormalities affecting the heart. Reports have been published on the long-term follow-up of surgical closure of the defect.[1-4] Much attention has been paid to specific aspects, especially conduction disturbances[5-11] and pulmonary vascular diseases[12-16] after surgery. Very little has been written about late death, and to our knowledge no paper in the English journals deals with ventricular arrhythmia and its relation to late death.

We report a series of 187 patients who were successfully operated on by W P Cleland and H H Bentall between 1958 and 1975 at the Hammersmith Hospital and who have been followed for one to 21 years after operation with special attention to factors relating to late deaths.

Subjects and methods

Hospital records of 187 patients, whose ventricular septal defects were closed between 1958 and 1975 and who survived for more than one year after operation were reviewed. Age at operation, year of operation, sex, anatomical site and size of the defect, mode of closure, haemodynamic data, postoperative heart failure, and infective endocarditis were noted and tabulated. The clinical status of survivors was determined either by direct contact with each patient or by questionnaires sent to the patients or their attending physicians.

Standard 12 lead electrocardiograms recorded preoperatively, postoperatively (period in hospital after surgery), and during the follow-up period were analysed and compared for the presence of arrhythmias, conduction disturbances, and mean frontal plane QRS axis. Left axis deviation was diagnosed when the mean frontal plane QRS axis was beyond −30°. Right bundle-branch block was considered present when the QRS interval in the right precordial leads exceeded 120 ms with a definite terminal delay. Ventricular ectopic activity found on routine electrocardiograms was graded as outlined in Table 1.

Twenty-four hour outpatient ambulatory electrocardiographic monitoring was performed on 51 unselected patients with the Oxford Medilog cassette recording system. Recordings were analysed using a Reynolds High Speed Pathfinder analyser. Ventricular arrhythmias were graded as outlined in Table 1 using a modification of the Lown criteria.[17] Subjec-

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Table 1 *Grading of ventricular arrhythmias*

Grade	*Routine electrocardiogram*	*24 hour electrocardiographic monitoring*	*Exercise test*
0	No ventricular extrasystoles	No ventricular extrasystoles	No ventricular extrasystoles
1	One ventricular extrasystole in less than 30% of available electrocardiograms	Occasional ventricular extrasystoles but no more than 30 in any hour of monitoring	One ventricular extrasystole per minute
2	One ventricular extrasystole in less than 30% of available electrocardiograms	More than 30 ventricular extrasystoles in any hour of monitoring	Two ventricular extrasystoles per minute
3	Multiform ventricular extrasystoles in addition to two	Multiform ventricular extrasystoles	Multiform ventricular extrasystoles
4a	Couplets in addition to two	Couplets	Couplets
4b	Ventricular tachycardia (salvoes of three or more ventricular extrasystoles)	Ventricular tachycardia	Ventricular tachycardia

tive maximal exercise testing was done on 38 unselected patients, 31 of whom also had 24 hour ambulatory electrocardiographic monitoring.

The exercise tests were performed in accordance with the Bruce protocol[18] on a motorised treadmill. The electrocardiogram, using Frank orthogonal leads (XYZ), was displayed on an oscilloscope and visually observed for rate and rhythm for at least 10 minutes before the exercise procedure. All arrhythmias seen during this period were recorded. During, and for five minutes after exercise, a standard electrocardiographic strip chart recorder continuously recorded these three leads. Indirect blood pressure determinations were done before and immediately after exercise. In the absence of disabling fatigue, dyspnoea, angina pectoris, or major ventricular arrhythmia (sustained ventricular tachycardia or ventricular fibrillation), the patients were encouraged to continue for as long as possible. Grading of ventricular arrhythmias was performed using the criteria of Antman *et al.*[19] as outlined in Table 1.

Statistical analyses were done using the χ^2 test.

Results

Of the 187 patients reported here, 102 were male and 85 female. There were 147 children whose ages ranged from 2 to 16 years. The mean age at operation was 12·6 years, range two to 44 years. The mean follow-up period was 11 years, with a range of one to 21 years. There were 17 late deaths one to 21 years after operation.

The defect was considered "large" in 167 patients and "small" (<1 cm) in 20 patients. The defects were membranous in 134 patients, infundibular in 20 patients, muscular in five, in the inflow septum in eight, a Gerbode type defect in 13, and multiple in seven. The defect was patched in 95 patients and closed by sutures alone in 92.

ASSOCIATED DEFECTS AND RESIDUAL LESIONS

In addition to closure of the ventricular septal defect, 38 patients, with gradients ranging from 20 to 60 mmHg across the right ventricular outflow tract, had resection of infundibular muscle. Three patients had atrial septal defects closed and eight had a persistent ductus arteriosus ligated. Nineteen patients had associated aortic regurgitation. The defects in the latter patients were membranous in nine, infundibular in nine, and a left ventricular to right atrial shunt in one.

Three of them had a sinus of Valsalva fistula to the right ventricle and three had small perforations of one of the aortic cusps. All of these were closed during surgery. Thirteen patients had a right or non-coronary cusp prolapsing through the ventricular septal defect, requiring valvuloplasty in all.

The aortic regurgitation was considered mild in 10 patients, moderate in five, and severe in four. Fifteen of these patients still had aortic regurgitation after surgery. Additionally, eight patients who did not have aortic regurgitation preoperatively, developed it postoperatively, making the total with postoperative aortic regurgitation 23. In the majority (15) the postoperative aortic regurgitation was mild to moderate and remained stable during the follow-up period. Two of those, though completely asymptomatic, died unexpectedly three and 15 years after operation. In both there was reason to believe that death resulted from complete heart block.

In eight patients aortic regurgitation was progressive with left heart failure. Five of these had one or more episodes of infective endocarditis. One of them died before valve replacement could be done and three others two weeks to six months after aortic valve replacement. One is alive and asymptomatic after aortic valve replacement. Thus, a total of seven deaths occurred in the group with postoperative aortic regurgitation, four of whom had infective endocarditis as well.

On clinical grounds 43 patients were thought to have signs of residual ventricular septal defect after operation, five associated with residual aortic regurgitation and two with mitral regurgitation. In 37 the residual defect was considered insignificant, but in six it required reclosure of the defect.

ENDOCARDITIS

During the follow-up period, 10 patients had one or more episodes of infective endocarditis. Four of these had residual ventricular septal defect, four had aortic regurgitation, and one had ventricular septal defect and aortic regurgitation. The remaining patient is of interest as he had well documented, culture positive, infective endocarditis without signs of any residual lesions.

MYOCARDIAL INFARCTION

Four patients had myocardial infarctions. Two of them had residual aortic regurgitation and one residual ventricular septal defect, all three requiring reoperation. In one the infarction followed the original operation and in two it followed reoperation. The remaining patient had pulmonary hypertension with no residual lesions and had a myocardial infarction 19 years after operation at the age of 26. All four died.

HEART FAILURE

Nineteen patients were treated for left heart failure during the follow-up period. One of them had progressive pulmonary hypertension and myocardial infarction, one was dignosed as peripartum cardiomyopathy, one had progressive pulmonary hypertension only, and the remaining 16 all had residual ventricular septal defect and/or aortic regurgitation complicated by a myocardial infarction in one and infective endocarditis in seven. Eight of the patients who had heart failure and four who had infective endocarditis during the follow-up period died.

HAEMODYNAMICS

One hundred and three patients had preoperative systolic pulmonary artery pressures above 40 mmHg. Table 2 summarises the systolic pulmonary artery pressure:systemic artery pressure ratio, and Table 3 the pulmonary arteriolar resistance in these patients.

There were 12 late deaths in this group (cases 1, 5, 6, 7, 8, 9, 11, 12, 13, 14, 16, 17, Table 4) but only three of them (cases 1, 7, 9) had progressive pulmonary vascular disease and their deaths were largely the result of this, though one also had complete heart block (case 9) and one had a myocardial infarction and serious ventricular arrhythmias (case 7).

Patients with raised pulmonary artery pressure and resistance did not have a significantly increased incidence of conduction disturbances or ventricular arrhythmias. The functional status of patients with pulmonary vascular disease has been previously reported.[12 13]

CONDUCTION PATTERNS

Conduction disturbances were common after closure of a ventricular septal defect. In all our patients the defect was closed via a ventriculotomy so that comparison with other surgical techniques was not possible.

Fig. 1 summarises the various conduction patterns found preoperatively, postoperatively, and on the last available electrocardiogram during the follow-up period. The figures in brackets are the numbers of late deaths.

Preoperatively there were 10 patients with left axis deviation and 12 with right bundle-branch block. Two of these had left axis deviation plus right bundle-branch block and one had right bundle-branch block, left axis deviation, and first degree atrioventricular block.

Postoperatively there was a total of 105 (56%) patients with right bundle-branch block and 26 (14%) with left axis deviation alone or in combination. Subsequently, a further 14 developed right bundle-branch block and 16 left axis deviation. This is partly accounted for by 14 of the patients who had transient second degree atrioventricular block or complete heart block postoperatively. Three of these were left with left axis deviation, right bundle-branch block, and first degree atrioventricular block, four with left axis deviation plus right bundle-branch block, three with first degree atrioventricular block and right bundle-branch block, and four with right bundle-branch block alone. There remains a group of nine patients who developed left axis deviation one to 10 years postoperatively, having previously had normal

Table 2 *Preoperative systolic pulmonary artery: systemic artery pressure ratio in 103 patients with systolic pulmonary artery pressure >40 mmHg*

Pressure ratio	0·3	0·4	0·5	0·6	0·7	0·8	0·9	1	>1
Number	11	18	12	15	7	11	8	19	2

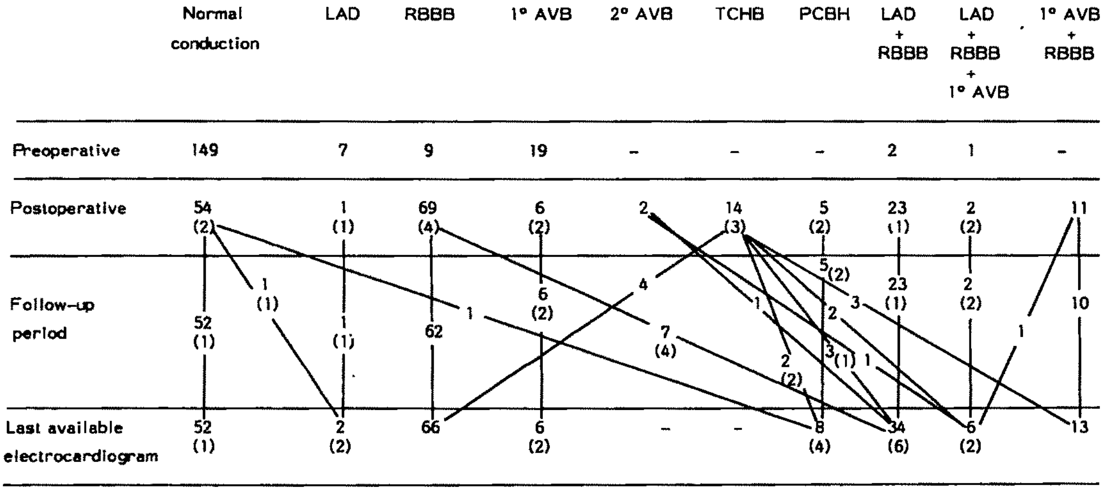
Table 3 *Preoperative pulmonary arteriolar resistance in 103 patients with systolic pulmonary artery pressure >40 mmHg*

Pulmonary arteriolar resistance	2	2·1–3	3·1–4	4·1–5	5·1–7	7·1–10	10·1–15	>15	?
No.	24	14	10	8	7	23	9	5	3

Table 4 *Clinical, haemodynamic, and electrocardiographic data of 17 late deaths*

Case No.	*Age (y)*	*Anatomy*	*Residual defect*	*Indication reoperation*	*Preop*	*Preoperative ECG*			*Postoperative ECG*					*Postop survival (y)*	
					PAR (units)	*LAD*	*RBBB*	*AV cond.*	*Rhythm*	*LAD*	*RBBB*	*AV cond.*	*Rhythm*		
1	5	Large muscular	No.	—	10	No	Yes	N	NSR	Yes	Yes	N	NSR	15	Progressive pulmonary vascular disease
2	27	Membraneous	AR	HF	4	No	No	1°	NSR	No	No	1°	NSR	4	Operative death
3	39	Membraneous VSD, AR	AR	AR, HF	0·8	Yes	No	N	AF 4b	Yes	No	N	4b	7	SBE postop., died of VF one month after aortic valve replacement
4	32	Membraneous AR	AR	AR, SBE, HF	1·7	No	No	1°	NRS	No	No	1°	3	3	AMI after aortic valve replacement; died of VF one month later
5	21	Infundibular AR	AR	AR, SBE, HF	3·6	No	No	N	1	Yes	No	N	AF 4b	3	AMI postop.; repeated angina pectoris; after aortic valve replacement typical Adams–Stokes attacks; sudden death on pavement
6	36	Gerbode AR	AR	—	3·8	Yes	Yes	1°	NSR	Yes	Yes	AF	AF 4b	2	Increasing AR and HF; sudden death in hospital —VF
7	7	Membraneous	—	—	1·3	No	Yes	N	NSR	Yes	Yes	N	4a	21	PPVD; AMI 19 years post-op; sudden death
8	41	Membraneous	VSD	HF, VSD	1·6	Yes	Yes	1°	NSR	Yes	Yes	1°	1	4	AMI after reclosure VSD; died one month post-op—VF
9	13	Infundibular	VSD	—	1·8	No	Yes	3° (temp)	—			3°	3	16	Increasing PPVD; sudden death at home
10	6	Membraneous AR	VSD	—	0·8	Yes	Yes	N	NSR	Yes	Yes	N	4a	16	Did well; physical sport; unexpected sudden death
11	14	Membraneous	VSD	—	2·0	No	No	N	NSR	No	No	N	NSR	1	Anaesthetic death; documented VF
12	18	Membraneous	VSD (small)	—	1·6			T3°	4b	Yes	Yes	1°	AF 4a	6	Sudden unexpected death at home
13	10	Inflow	—	—	?	No	Yes	N	NSR	Yes	Yes	N	AF 4b	3	Sudden death from VF during anaesthesia
14	15	Infundibular	AR	—	?			3°	—			T3°		3	Sudden death after mild respiratory infection
15	4	Membraneous PDA	VSD, AR	—	?			T3°	—			T3°	—	15	Transient CHB at re-catheter; sudden death one month later
16	7	Infundibular	—	—	5·1			3°				3°		1	Asymptomatic; sudden death at home
17	44	Membraneous	—	—	2·9	No	Yes	N	NSR	Yes	Yes	N	AF	9	Mild heart failure; sudden death

AR, aortic regurgitation; HF, heart failure; SBE, infective endocarditis; NSR, normal sinus rhythm; AF, atrial fibrillation; PAR, pulmonary arteriolar resistance; AMI, acute myocardial infarction; PPVD, progressive pulmonary vascular disease; LAD, left axis deviation; RBBB, right bundle-branch block; VSD, ventricular septal defect; PDA, persistent ductus arteriosus; VF, ventricular fibrillation; CHB, complete heart block.



Figures in brackets indicate number of deaths.

Abbreviations: LAD = left axis deviation; RBBB = right bundle-branch block; AVB = atrioventricular block; TCHB = temporary complete heart block; PCHB = permanent complete heart block.

Fig. 1 *Conduction patterns on preoperative, postoperative, and last available electrocardiogram.*

conduction in one, right bundle-branch block alone in seven, and first degree atrioventricular block and right bundle-branch block in one. Five of these patients with progressive conduction defect died (cases 1, 5, 7, 13, and 17). Two patients with transient complete heart block postoperatively developed complete heart block again, one (case 9) 13 years after operation and the other (case 15) developed transient complete heart block again 15 years later during recatheterisation. Both these patients subsequently died. One patients with normal conduction postoperatively later developed first degree atrioventricular block and 15 years postoperatively he had a few fainting spells. During one of these an electrocardiogram was done which showed a transient complete heart block. He was Holter monitored and, during the 24 hours, he had normal conduction alternating with first, second, and third degree atrioventricular block. He has had a pacemaker implanted and is now free of symptoms.

RHYTHM DISTURBANCES

Table 5 gives a detailed analysis of the ventricular arrhythmias detected on routine electrocardiogram during the follow-up period in the whole group and correlates it with the conduction pattern in each patient. The number of late deaths is indicated by the bottom figure in brackets in each column. One hundred and forty-eight patients had no ventricular arrhythmias. Six of these patients died. Three of them had complete heart block (cases 14, 15, and 16, Table 4), one had a first degree atrioventricular block (case 2), and two had uncomplicated sinus rhythm (cases 1 and 11).

Table 5 *Ventricular arrhythmia (grade) vs conduction on routine electrocardiograms during follow-up period*

Conduction	*Ventricular arrhythmia*						
	0	*1*	*2*	*3*	*4a*	*4b*	*Total*
Normal	48 (1)	1	1	1			52 (1)
LAD						2 (2)	2 (2)
RBBB	53	8	4	1			66 (0)
1° AV block	4 (1)			1 (1)		1	6 (2)
1° AV block +RBBB	9	1		3			13 (0)
LAD+RBBB	26 (1)	2	1	1 (1)	3 (3)	1 (1)	34 (6)
1°x AV block+ LAD+RBBB	2	1 (1)		1	1	1 (1)	6 (2)
CHB	6 (3)		1	1 (1)			8 (4)
Total	148 (6)	14 (1)	7 (0)	9 (3)	4 (3)	5 (4)	187 (17)

Figures in brackets indicate number of late deaths.
Abbreviations: Fig. 1. Grading: As in Table 1.

Fourteen patients had grade 1 ventricular arrhythmia. Only one of these patients (case 8), who also had left axis deviation, right bundle-branch block, and first degree atrioventricular block, died.

Seven patients had grade 2 ventricular arrhythmia. There were no late deaths in this group.

Nine patients had grade 3 ventricular arrhythmia, three of whom died. One of the deaths had an associated first degree atrioventricular block (case 4), one a complete heart block (case 9), and one had left axis deviation plus right bundle-branch block (case 17).

Four patients had grade 4a ventricular arrhythmia. Three of these died (cases 7, 10, and 12); all three also had left axis deviation plus right bundle-branch block.

Five patients had grade 4b ventricular arrhythmia, four of whom died. Two of these (cases 3 and 5) had left axis deviation and two (cases 6 and 13) had left axis deviation plus right bundle-branch block.

Eleven patients had supraventricular arrhythmias during the follow-up period. In six this was established atrial fibrillation, while five others had paroxysmal atrial fibrillation or atrial tachycardia. Five of the patients with supraventricular arrhythmias died, but all had ventricular arrhythmias as well. Three had grade 4b, one had grade 4a, and one had grade 3 ventricular arrhythmia.

Patients with conduction defects had a significantly increased incidence of ventricular arrhythmias of all grades ($p<0.003$).

LATE DEATHS

Seventeen patients died one to 21 years after operation. They were all operated upon before 1968. Table 4 summarizes the clinical, electrocardiographic, and haemodynamic findings in these patients.

In five (cases 3, 6, 8, 11, and 13) the immediate cause of death was documented as ventricular fibrillation in hospital. In nine more the terminal events strongly suggested death from arrhythmia. The remaining three patients died of progressive pulmonary vascular disease (case 1), intraperitoneal haemorrhage after aortic valve replacement (case 4), and during surgery for aortic valve replacement (case 2).

Cases 1 and 2, who died from causes other than arrhythmias, did not have any documented ventricular arrhythmias, while case 4 had grade 3 ventricular arrhythmia.

Only one of the patients who died of arrhythmia (case 11) had normal conduction and no ventricular arrhythmias documented during the follow-up period, but there was only one electrocardiogram available for analysis. The remaining 13 arrhythmic deaths all had ventricular arrhythmias and/or conduction defects during the follow-up period. (This has already been discussed.) The risk of late death was significantly increased by the presence of grade 3–4b ventricular arrhythmia ($p<0.001$).

On clinical grounds the late deaths could be divided into a group of eight patients in whom death was sudden and unexpected, and nine in whom death was not unexpected.

EXPECTED LATE DEATHS

(cases 1, 2, 3, 4, 5, 6, 7, 8, 9, Table 4)

These patients had a mean age of 25·4 years at operation (range five to 41 years).

Three had progressive pulmonary vascular disease and falling cardiac output (cases 1, 9, and 7) complicated in case 9 by residual ventricular septal defect and complete heart block and in case 7 by grade 4b ventricular arrhythmia, left axis deviation and right bundle-branch block, and a myocardial infarction. They died respectively 15, 16, and 21 years after operation.

Four patients (cases 3, 4, 5, and 6) had postoperative aortic regurgitation, one had aortic regurgitation and residual ventricular septal defect (patient 2), and two had residual ventricular septal defect (patients 8 and 9). In five of these the residual lesions required reoperation (cases 2, 3, 4, 5, and 8). Three of these patients (cases 4, 5, and 8) also had myocardial infarctions. Case 5 had an extensive anterior infarction after the original operation. He had repeated attacks of angina pectoris after discharge, increasing aortic regurgitation and left heart failure necessitating aortic valve replacement three years later. After this operation he had repeated classical Adams-Stokes attacks and died during one of them six months later. Cases 4 and 8 had myocardial infarction after reoperation for aortic valve replacement (case 4) and closure of residual ventricular septal defect (case 8). Both died in hospital within one month of operation. Four of the late deaths with residual lesions were also treated for infective endocarditis (cases 3, 4, 5, and 6) during the follow-up period.

SUDDEN UNEXPECTED DEATHS

The patients in this group had a mean age of 13·7 at operation. Only one (case 17) had signs of mild heart failure during the last four years of follow-up. After operation he had atrial fibrillation and right bundle-branch block. He gradually developed left axis deviation over the following six years. He also had grade 3 ventricular arrhythmia and died suddenly at home nine years after operation. He complained of palpitation two weeks before death.

Four patients developed complete heart block after operation (cases 12, 14, 15, and 16). In two the block was permanent. One of them (case 14) developed mild aortic regurgitation two weeks after operation and died suddenly three years after operation after a mild respiratory infection. The other patient (case 16) with permanent complete heart block died suddenly at home one year after operation. He had pulmonary hypertension and raised pulmonary arteriolar resistance but was completely asymptomatic. Case 15 had a small ventricular septal defect and mild aortic regurgitation. He was asymptomatic but redeveloped transient complete heart block 15 years after closure of his ventricular septal defect during a catheterisation procedure and died suddenly one month later at home.

The other patient with transient postoperative complete heart block (case 12) had a small residual ventricular septal defect but was asymptomatic. His follow-up electrocardiogram showed right bundle-branch block, left axis deviation, and first degree atrioventricular block complicated by grade 4a ventricular arrhythmia. He died suddenly at home. Case 11 had normal conduction and no ventricular arrhythmias noted during follow-up. He was asymptomatic and died of documented ventricular fibrillation during anaesthesia for a fractured forearm one year after operation.

Case 13 had frequent attacks of paroxysmal supraventricular tachycardia. He also had left axis deviation, right bundle-branch block, and grade 4b ventricular arrhythmia and died of ventricular fibrillation during anaesthesia for a dental extraction three years after closure of his ventricular septal defect.

Finally, case 10 had a small residual ventricular septal defect but was completely asymptomatic. He had left axis deviation, right bundle-branch block, and grade 4a ventricular arrhythmia. He died suddenly at home, presumably from a ventricular tachyarrhythmia.

TWENTY FOUR HOUR AMBULATORY ELECTROCARDIOGRAPHIC MONITORING

Continuous 24 hour monitoring was performed on 51 unselected patients 10 to 20 years (mean 14 years) after operation. Table 6 correlates the highest grade of ventricular arrhythmia with the conduction pattern on the 12 lead electrocardiogram. Fig. 2 compares the ventricular arrhythmias detected on continuous 24 hour monitoring with those found on the routine electrocardiograms.

Nineteen patients had ventricular arrhythmias during the 24 hours of monitoring. In eight of them, the arrhythmia was Lown grade 3–4b. All the patients with ventricular arrhythmia had conduction disturbances. Two of the patients with grade 4a ventricular arrhythmia have subsequently died, one of them unexpectedly. Three patients had progressive conduction defect. All of them had ventricular arrhythmias and one died. Thirty-two patients had no ventricular arrhythmias, 16 of them had normal conduction, and 16 had conduction disturbances.

EXERCISE TEST

Exercise testing was done on 38 unselected patients. Table 7 correlates the ventricular arrhythmias according to the Antman criteria with the conduction pattern on the 12 lead electrocardiogram. Fig. 3 compares the higest grade of ventricular arrhythmia found on exercise with that on continuous 24 hour monitoring in the 31 patients who had both tests.

Sixteen patients had ventricular arrhythmias during or immediately after exercise, five of them grade 3 or

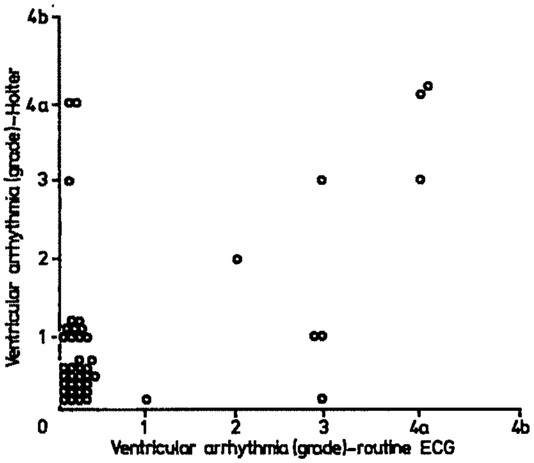


Fig. 2 *Ventricular arrhythmia—24 hour continuous electrocardiographic monitoring versus routine electrocardiogram.*

Table 6 *24 hour ambulatory electrocardiographic monitoring: ventricular arrhythmia (grade) vs conduction*

Grade	*Conduction*						
	Normal	*RBBB*	*LAD+ RBBB*	*LAD+ 1° AV block+RBBB*	*PCD*	*CHB*	*Total*
0	16	7	8	—	—	1	32
1	—	3	5	—	1	1	10
2	—	—	—	—	1	—	1
3	—	1	1	1	—	—	3
4a	—	2	1	—	1	—	4
4b	—	—	1	—	—	—	1
Total	16	13	16	1	3	2	51

Abbreviation: PCD, progressive conduction defect.
Other abbreviations as in Fig. 1.

Table 7 *Exercise test: ventricular arrhythmia (grade) vs conduction*

Grade	*Conduction*					
	Normal	*RBBB*	*LAD+RBBB*	*LAD+1°AV block +RBBB*	*CHB*	*Total*
0	9	6	6	—	1	22
1	1	2	3	—	1	7
2	—	—	3	1	—	4
3	—	2	1	—	—	3
4a	—	—	—	—	—	0
4b	—	1	1	—	—	2
Total	10	11	14	1	2	38

Abbreviations as in Fig. 1.

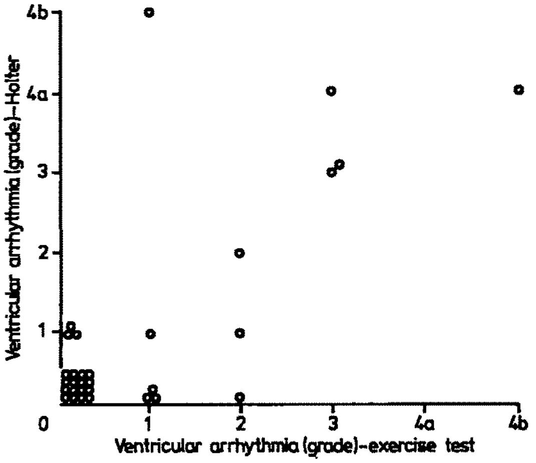


Fig. 3 *Ventricular arrhythmia—24 hour continuous electrocardiographic monitoring versus exercise.*

higher. Fifteen of the patients with ventricular arrhythmia had conduction disturbances as well.

Twenty-two patients had no ventricular arrhythmias on exercise. Nine of them had normal conduction and 13 had conduction disturbances.

Discussion

Conduction disturbances after surgical closure of ventricular septal defect has been recognised as the most common complication of this operation.[5,6,8,10,11] Right bundle-branch block has been reported to occur in 31 to 70% of cases repaired via a ventriculotomy,[5,6,9,20,21] and left axis deviation in six to 47%[6,9,10,22] of cases. Sixty-three per cent of our patients had right bundle-branch block and 22·4% had left axis deviation on their last available electrocardiogram. If we omit the 10 patients who already had left axis deviation preoperatively, 17·1% acquired left axis deviation as a result of operation. We had 9 patients who developed left axis deviation one to 10 years after operation. Five (55·6%) of these patients with progressive conduction defect died, compared with the four late deaths (15·3%) in the group of 26 patients who already had left axis deviation postoperatively. To our knowledge this has not been reported previously. Quattlebaum *et al.*[22] state that 56% of their patients who had right bundle-branch block and left axis deviation developed the left axis deviation one to seven years after correction of tetralogy of Fallot, but they do not correlate this with sudden late death.

Concern about the possible late development of complete heart block in patients with left axis deviation and right bundle-branch block has been expressed.[5,6,11] Downing *et al.*[10] believe that this combination does not carry a bad prognosis in children but contend that the ultimate prognosis is undetermined. Wolff *et al.*[24] and Godman *et al.*[11] found a high percentage of patients developing late complete heart block had this combination previously. Godman suggests that the patients most likely to develop late complete heart block are those who have transient complete heart block postoperatively and who have left axis deviation and right bundle-branch block on return to sinus rhythm.

Our study lends some support to this view. Three of our patients developed late complete heart block. Two of them had transient complete heart block postoperatively and were left with left axis deviation and right bundle-branch block. The remaining patient had normal conduction and developed complete heart block 15 years after operation. Complete heart block is relatively common after operation[2,6,8,9,22] but is usually a transient phenomenon.[2,8,22]

A high mortality rate of up to 57% has been reported for patients with permanent complete heart block.[2] Fourteen of our patients had transient complete heart block postoperatively, with three deaths (21%). Five patients had postoperative complete heart block that persisted, two (40%) of whom died. There were 20 patients, including the patient who developed complete heart block for the first time 15 years after operation, who had complete heart block at some stage, with five late deaths (25%).

In the light of our findings, late sudden death in patients with transient or permanent complete heart block after surgical repair of ventricular septal defect should not be unexpected. Implantation of permanent pacemaker should be considered in all cases.

Much has been written about the cause of the various conduction defects of surgical closure of ventricular septal defect[5 6 10 20 21 23 25–27]. It has been ascribed to the ventriculotomy,[5 25 26] to direct trauma to the conducting tissue by the placement of sutures around the defect,[6 21 27] or to the resection of infundibular muscle in cases where this is required.[28] Our study does not throw new light on this problem, but we tend to agree with Okoroma *et al.*[20] and Downing *et al.*[10] that all these mechanisms can produce conduction disturbances in their own right.

James *et al.*[29] and Rosing *et al.*[30] considered ventricular arrhythmias to be a more important cause of sudden death than complete heart block after correction of tetralogy of Fallot. Our findings strongly support those of Wolff *et al.*[24] and Quattlebaum *et al.*[22] who found a significant association between ventricular arrhythmias, conduction defects, and sudden death during the long-term follow-up after surgical correction of tetralogy of Fallot.

On routine electrocardiograms, 39 (20·8%) had ventricular arrhythmias of all grades during the follow-up period. Eleven of these (28%) died, 10 of them having grade 3–4b ventricular arrhythmias.

There was also a striking correlation between conduction defects and ventricular arrhythmias ($p<0{\cdot}003$). Of the 52 patients with normal conduction during the follow-up period, four (7·7%) had ventricular arrhythmias of all grades, while 26% of the 135 patients who had any form of conduction disturbance had ventricular arrhythmias detected on their routine electrocardiograms. Of the patients with progressive conduction defects, 66% had ventricular arrhythmias.

On continuous 24 hour monitoring not one of the 14 patients with normal conduction had any ventricular arrhythmias, while 53% of the patients with conduction defects had ventricular arrhythmias during the 24 hour period of monitoring. This is statistically significant ($p<0{\cdot}001$). The overall incidence of ventricular arrhythmias detected on continuous 24 hour monitoring was 37·3%. Deanfield *et al.*,[31] reporting a similar study on postoperative tetralogy of Fallot, found that 80% of patients with progressive conduction defects had ventricular arrhythmias. We could only monitor three patients with progressive conduction defects, and it is of interest that they all had ventricular arrhythmias and that one of these has since died, but the numbers involved are too small to make any firm conclusions.

On exercise testing only one of 10 patients (10%) with normal conduction had ventricular arrhythmias, while 15 of the 28 patients (53·6%) with conduction defects had ventricular arrhythmias ($p<0{\cdot}02$). In all, 39·5% of patients had ventricular arrhythmias on exercise. The incidence of ventricular arrhythmias found in our patients with continuous 24 hour monitoring and exercise testing is considerably greater than that found in similar studies of comparable subjects without heart disease.[32] This significant association of ventricular arrhythmias with conduction disturbances, particularly with progressive conduction defects, suggests that the same mechanism is responsible for both. Deanfield *et al.*[31] speculated that this may be the result of granulomata induced by suturing. Wolff *et al.*[24] suggested that the development of complete heart block with bradycardia makes the heart more vulnerable to ventricular arrhythmias. Our study does not support this, as none of our patients who had ventricular arrhythmias detected by any of the three methods used had complete heart block at the time that their ventricular arrhythmias occurred, though this may have been the terminal factor in some of our patients who died late.

In the individual patient, there was not a good correlation of the grade of ventricular ectopic activity detected by the three methods we used. All three methods adjunctively disclosed more ventricular ectopy than any method alone.

Although the prognostic value of ventricular arrhythmias detected with continuous 24 hour electrocardiographic monitoring and exercise testing remains to be determined, two of the patients with grade 4a ventricular arrhythmia on continuous 24 hour monitoring have since died, one of them unexpectedly. These two patients did not have an exercise test, but both had grade 4a ventricular arrhythmia on their routine electrocardiograms.

The association of ventricular septal defect and aortic regurgitation is well recognised, with a reported incidence of 3 to 7%.[33 34] Postoperative aortic regurgitation worsened the prognosis considerably, with seven late deaths in 23 cases. In common with other workers we found an increased risk of infective endocarditis in patients with residual aortic regurgitation. Four of the five expected deaths with aortic regurgitation had had infective endocarditis during the follow-up period. Other workers have found that, in the majority of patients with residual aortic regurgitation, the regurgitation remains stable after operation.[34] In 15 of our 23 patients with postoperative aortic regurgitation, the regurgitation was mild and remained stable. Five of the eight patients in whom the aortic regurgitation was progressive had infective endocarditis contributing to this progression.

Finally, it should be noted that great improvement

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in surgical technique and myocardial protection during operation has occurred in recent years. Since all our late deaths were operated on before 1968 similar series in future should yield better results.

Conclusions

There is a significant incidence of unexpected sudden death up to 21 years after surgical closure of ventricular septal defect and a high percentage of patients develop conduction disturbances after operation. Especially important are those who develop left axis deviation during the follow-up period, as they have a high mortality rate. Complete heart block during the follow-up period has a grave prognosis. Ventricular arrhythmias are common during the follow-up period. they occur significantly more frequently in patients with conduction disturbances, and grades 3 to 4b particularly are reliable predictors of late death. The death in two patients as a result of ventricular fibrillation during anaesthesia for minor surgery suggests that anaesthesia after repair of ventricular septal defect should be given only in centres where full and immediate resuscitative facilities are available. The prognostic value of exercise testing and 24 hour ambulatory electrocardiographic monitoring has not been established after closure of ventricular septal defect, but, in view of the importance of ventricular arrhythmias, we strongly advocate that these tests should be done serially on all patients.

It remains to be proved that treatment of ventricular arrhythmias will prevent sudden death, but the evidence suggests that preventative treatment should be arranged, especially in those patients who have been shown to be particularly vulnerable to these arrhythmias.

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Ventricular septal defects
Two dimensional echocardiographic and morphological correlations

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SUMMARY To evaluate the ability of two dimensional echocardiography to identify and classify ventricular septal defects, 280 infants and children with clinically significant ventricular septal defects were studied. Multiple precordial and subcostal echocardiographic planes were scanned in each patient in an attempt to identify the defects. Defects visualised were classified on the basis of the structures which formed their margins. Subsequent correlation of this information with angiographic (280 patients), surgical (130 patients), and pathological (31 patients) data confirmed that defects in the following sites produced a specific two dimensional echocardiographic pattern. (a) Perimembranous inlet, (b) perimembranous outlet, (c) muscular inlet, (d) single trabecular, (e) muscular outlet, and (f) doubly committed subarterial. A defect was identified and correctly classified in 252 patients. Individual defects were identified with varying degrees of accuracy. All subarterial (24 patients) defects were correctly identified and classified, as were muscular defects of the inlet (18 patients) and outlet (six patients) septa. Of the 185 perimembranous defects, 182 were identified. Only 23 of the 43 single trabecular defects were identified. Small multiple ("Swiss cheese") defects (four patients) were not identified.

We conclude that two dimensional echocardiography provides a reliable non-invasive method of identifying and classifying the following ventricular septal defects: (a) perimembranous defects, (b) doubly committed subarterial defects, and (c) muscular defects of the inlet and outlet septa. In our experience it fails consistently to visualise defects in the trabecular septum.

When investigating a ventricular septal defect it is not enough simply to diagnose the presence of a hole in the ventricular septum. The ideal investigative technique should consistently identify the defect and should define its site, its size, and the structures forming its margins, thus providing the information that will allow accurate morphological classification. Two dimensional echocardiography ought to provide this information, as the precision of the technique is such that it can image cardiac morphology in detail and can identify small defects in the ventricular septum.[1-3] It should therefore be possible to classify defects by determining whether they are (i) roofed in part by the central fibrous body and aortic valve (perimembranous defects), (ii) are entirely surrounded by muscle (muscular defects), or (iii) are roofed by conjoint aortic and pulmonary valves (doubly committed subarterial defects). This report describes an echocardiographic investigation of 280 patients known to have ventricular septal defects in one or other of these sites and the morphological studies carried out to validate our echocardiographic classification.

Subjects and methods

Two hundred and eighty patients with clinical evidence of ventricular septal defect, existing as either an isolated lesion or as part of a complex malformation, were studied by two dimensional echocardiography. The echocardiograms were recorded using either a

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2·4 MHz Toshiba phased array sector scanner or a 3·0 or 5·0 MHz Advanced Technology Laboratories mechanical sector scanner. The patients' ages ranged from day 1 of life (at 36 weeks gestation) to 17 years, with the majority of patients between the ages of 1 week and 7 years. All the patients attended either the Regional Cardiothoracic Unit, Freeman Hospital, The Hospital for Sick Children, Great Ormond Street, or the Royal Hospital for Sick Children, Edinburgh. In 31 patients the hearts were subsequently available for pathological sectioning and these were supplemented by the examination of selected hearts from the Cardiopathological Collection of the Cardiothoracic Institute, Brompton Hospital, London.

Of the 280 patients studied, 224 had a ventricular septal defect as the sole cardiac lesion. In the remaining 56 patients the septal defect was part of a more complex malformation such as tetralogy of Fallot (21 patients), double outlet right ventricle (17 patients), complete transposition (seven patients), truncus arteriosus (two patients), and pulmonary atresia (nine patients). These patients were included because the same echocardiographic information could be used to differentiate between perimembranous, muscular, or subarterial types of defect.

All patients had atrioventricular concordance. We excluded patients with any of the following lesions: (i) atrioventricular discordance, (ii) ambiguous atrioventricular connection, (iii) abnormal modes of atrioventricular communication (for example common, straddling, or imperforate atrioventricular valve), and (iv) univentricular heart, as in each of these the ventricular septal defect is only one component of a complex combined atrioventricular junction–septal malformation.

Patients were studied either prospectively or retrospectively. Group 1 comprised 149 patients who were known to have a ventricular septal defect from previous angiography. Group 2 comprised 131 patients who were studied prospectively and in whom the site of the defect was proven at subsequent angiography using the angled views of Soto *et al.*[4] Thus each patient had angiographic correlation of the presence of a defect. Of the patients, 130 had additional surgical description of their defect.

A standard echocardiographic procedure was used throughout the study. The heart was visualised from both the precordial and subcostal echocardiographic windows and the following standard echocardiographic planes[5] scanned and recorded, from the precordial approach (a) four chamber (apical and parasternal), (b) four chamber plus aortic root (apical and parasternal), (c) short axis of the great vessels, (d) short axis at ventricular level, (e) long axis and, subcostally (x) four chamber, (y) four chamber plus aortic root, and (z) right ventricular outflow (Fig. 1). An essential part of each investigation was a scan from one plane to another, building up in the process a three dimensional model of the heart.

The echocardiograms recorded were subsequently reviewed by a second investigator and the findings of both compared before a final decision was made as to the presence of a defect and its classification. (In patients already known to have a defect from previous angiographic investigation, the echocardiographer was unaware of the result of the earlier study.)

The two dimensional echocardiographic feature used to identify a ventricular septal defect was the presence of a discrete area of septal "drop out" persisting throughout systole and diastole in one or more of the echocardiographic planes recorded. In every case where such a defect was visualised an attempt was made to assess the extent of the defect by noting into which of the neighbouring echocardiographic planes it extended and to indentify the structures which formed its margins. Having determined the above echocardiographic features, defects could then be classified into one of the following morphological groups: (a) perimembranous defects, (b) muscular defects, or (c) doubly committed subarterial defects (Fig. 2).

This classification of ventricular septal defects is based on that proposed by Moulaert *et al.*,[6] subsequently modified by Soto *et al.*,[7] and further refined for use in this study.

MORPHOLOGICAL SUBDIVISION OF VENTRICULAR SEPTAL DEFECTS

(a) *Perimembranous defects*

These defects always involve the whole or part of the area which is occupied by the membranous septum in the normal heart. They are roofed in part by the central fibrous body and aortic root. Virtually all extend into one or more of the septal components which border the membranous septal area. Thus the whole group are referred to as perimembranous defects. These defects are subdivided depending on whether they extend primarily into the inlet, trabecular, or outlet septa (Table). Large perimembranous defects may involve all three of the surrounding septal components.

(b) *Muscular defects*

Defects surrounded entirely by muscular rims may be subdivided into those localised to the inlet, trabecular, or outlet components of the septum. Trabecular defects may be of single or multiple (Swiss cheese) types (Table).

(c) *Doubly committed subarterial defects*

The characteristic feature of these defects is that they

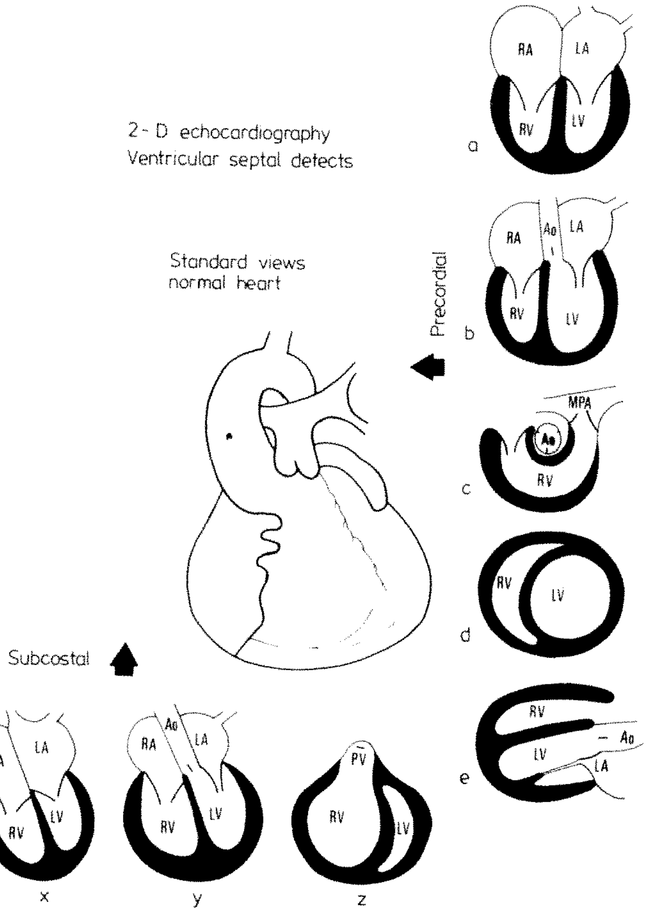


Fig. 1 *The two dimensional echocardiographic planes discussed in this study are as follows.* Precordial: *(a) four chamber; (b) four chamber plus aortic root; (c) short axis great vessels; (d) short axis at ventricular level; (e) left ventricular long axis.* Subcostal: *(x) four chamber; (y) four chamber plus aortic root; (z) right ventricular outflow tract (an identical sequence is used in Fig. 4b, 5b, 6b, 7b, 8b, and 10b). RA, right atrium; LA, left atrium; RV, right ventricle; LV, left ventricle; Ao, aorta; PV, pulmonay valve; MPA, main pulmonary artery.*

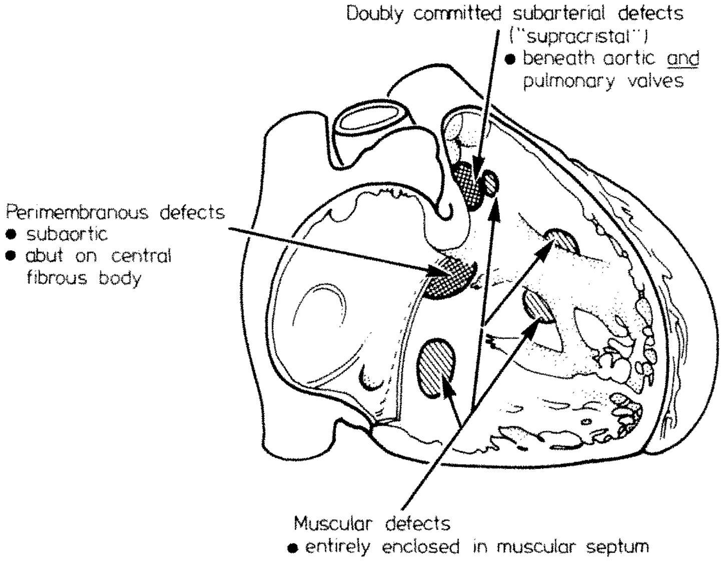

Doubly committed subarterial defects
("supracristal")
● beneath aortic and pulmonary valves
Perimembranous defects
● subaortic
● abut on central fibrous body
Muscular defects
● entirely enclosed in muscular septum

Fig. 2 *A diagram of the right ventricular septal surface illustrating the three main groups of defects.*

Table *Two dimensional echocardiography of ventricular septal defects*

Types of defect		*No. studied*	*No. correctly identified*	*% correctly identified*
Perimembranous (extending mainly into)				
(a) Inlet septum		43	43	100
(b) Outlet septum		84	83	98
(c) Trabecular septum		19	16	84
(d) All of the above		39	39	100
Muscular				
(a) Inlet		18	18	100
(b) Outlet		6	6	100
(c) Single trabecular	Large	32	23	72
	Small	11	0	0
(d) Multiple trabecular		4	0	0
Doubly committed subarterial				
(a) Not involving membranous septum		15	15	100
(b) Extending into membranous septal area		9	9	100
Total		280	252	

are roofed by aortic and pulmonary valve rings which lie at the same level and are in fibrous continuity. This abnormal situation is caused by absence of the normal infundibular septum which supports the pulmonary valve ring. Doubly committed subarterial defects may be subdivided into those that extend posteriorly to involve the membranous septum and those that are separated from it by a muscle bar (Table).

Having classified each ventricular septal defect on the basis of the two dimensional echocardiographic features, the results were then correlated with angiographic, surgical, and pathological findings to determine if individual defects could be reliably identified by a specific echocardiographic pattern.

Results

Correlation of the two dimensional echocardiographic information with the angiographic, surgical, and pathological findings disclosed that each type of ventricular septal defect was indentified by a specific echocardiographic pattern.

TWO DIMENSIONAL ECHOCARDIOGRAPHIC FEATURES WHICH DIFFERENTIATE SPECIFIC VENTRICULAR SEPTAL DEFECTS

(1) *Perimembranous defects* (185 patients)
In the normal heart the interventricular portion of the membranous septum is bounded superiorly by the atrioventricular portion of the membranous septum, anteriorly by the subaortic outlet septum, inferiorly by the trabecular septum, and posteriorly by the inlet septum. Two dimensional echocardiography will begin to visualise the two portions of the membranous septum at the most anterior extent of a scan through the four chamber plane (either precordial or subcostal) (Fig. 3). In addition, at the point at which this plane merges with the four chamber plus aortic root plane and the aortic valve is first visualised, the area of septum lying immediately below the aortic root is the interventricular membranous septum. It is consistently identified in the normal heart as a distinct short thin portion of the ventricular septum taking origin superiorly from the aortic root and expanding inferiorly to fuse with the much thicker trabecular system (Fig. 3). These features are better visualised from the subcostal than the precordial position, as the latter view foreshortens the extent of the membranous septum.

In 181 of the 185 perimembranous defects studied a discrete segment of septal echocardiographic drop out was recorded which involved the area of the interventricular membranous septum. In each of the 181 patients, the echocardiographic appearance clearly showed that the roof of this defect was that part of the aortic root which fused posteriorly with the central fibrous body. In the remaining four patients each with surgical confirmation of the type of defect (three with a perimembranous trabecular defect and one with a perimembranous outlet defect) the ventricular septum appeared intact in every echocardiographic plane.

In each of the 181 patients with a defect in the membranous septum, however, the area of septal drop out was found to extend into one or other of the neighbouring septal areas. Perimembranous defects could then be subdivided into four distinct groups on the basis of the differing echocardiographic patterns created by this extension of the defect.

(a) *Perimembranous inlet defects* (43 patients)
In every case the area of septal drop out involving the membranous septal area extended a variable distance posteriorly into the four chamber plane towards the crux of the heart. The roof of this posterior extension was formed by tissue separating the septal aspect of the tricuspid and mitral valve annuli (Fig. 4a). This tissue is comprised anteriorly of the central fibrous

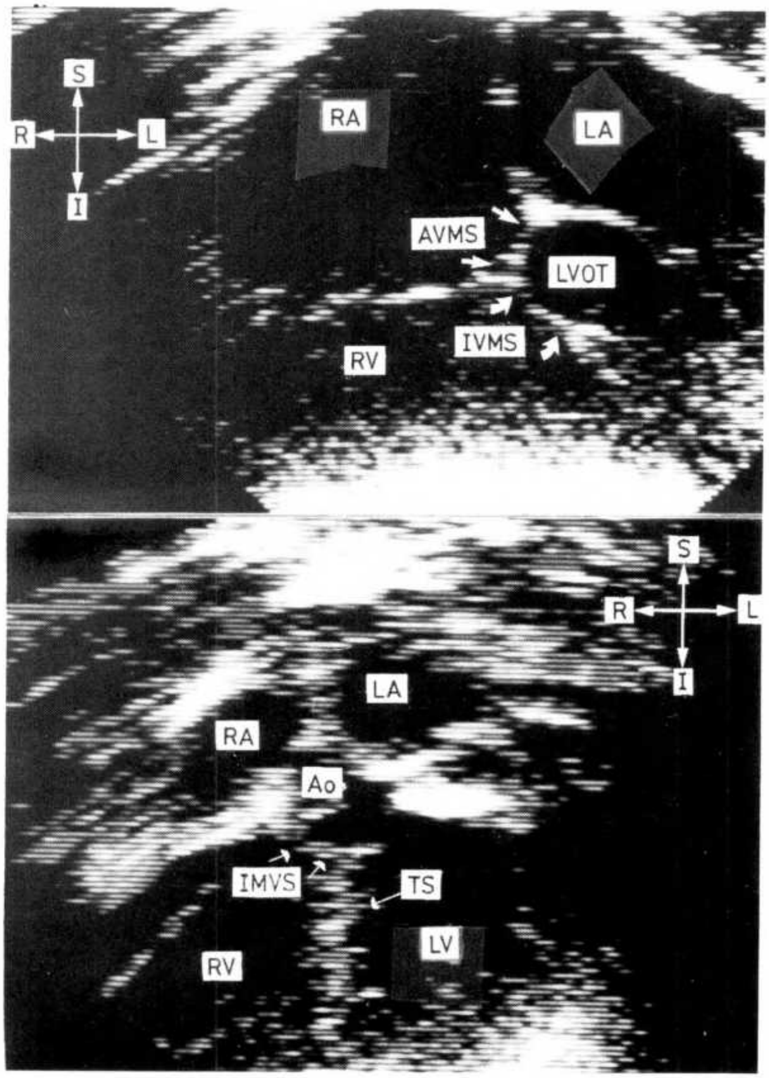
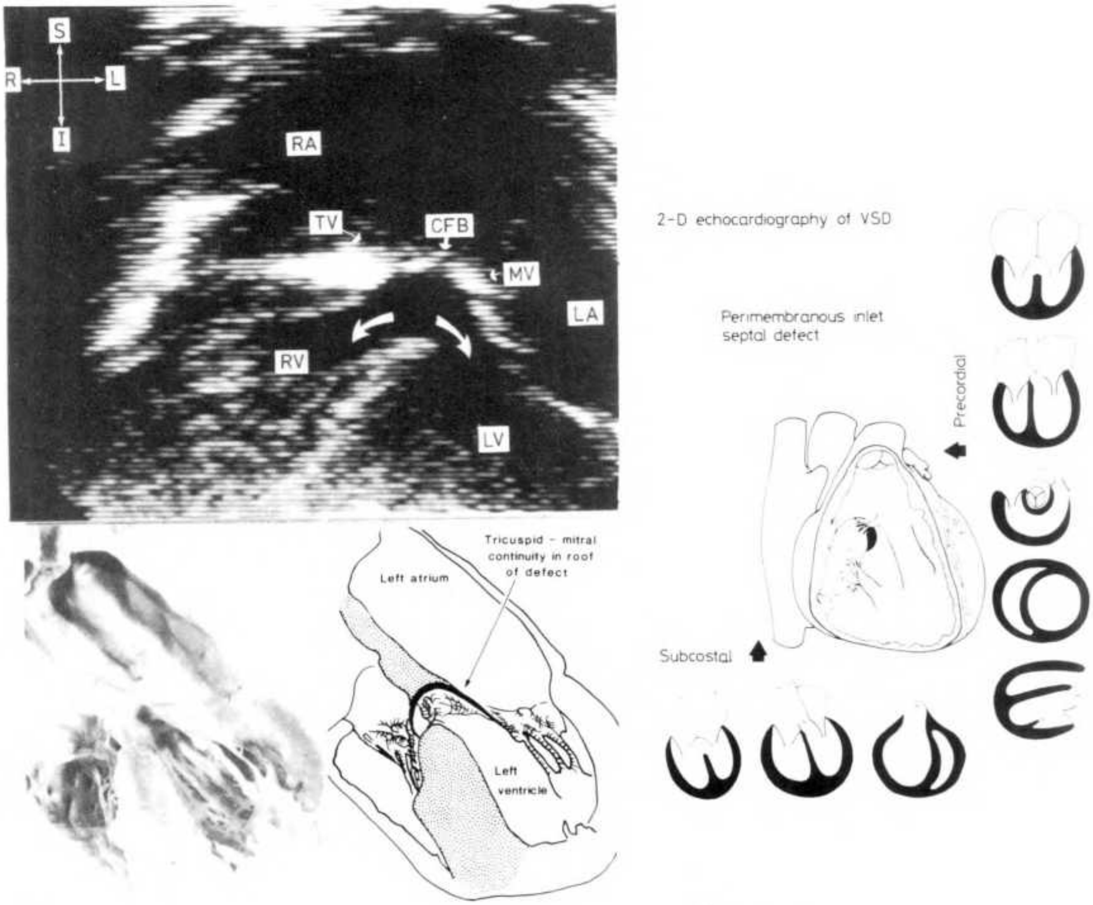


Fig. 3 *A normal intact membranous septum.* Upper panel: *a precordial four chamber plane at its junction with a four chamber plus aortic root plane. Straight arrows, atrioventricular membranous septum; curved arrows, interventricular membranous septum.* Lower panel: *a four chamber plus aortic root plane at aortic valve level. The interventricular membranous septum (arrowed) is bounded superiorly by aortic root and inferiorly by trabecular septum. Ao, aorta; LV, left ventricle; LVOT, left ventricular outflow tract; RV, right ventricle; RA, right atrium; LA, left atrium; TS, trabecular septum; AVMS, atrioventricular membranous septum; IVMS, interventricular membranous septum.*

body and atrioventricular muscular septum and posteriorly by the septal atrioventricular fibrous plane. In every case two dimensional echocardiography clearly showed that there was no remnant of inlet muscular septum projecting downwards from the atrioventricular junction to roof the defect.

Perimembranous inlet defects were consistently visualised (Table) using both the subcostal and precordial four chamber planes. In our experience, where the septum appears intact throughout a four chamber scan this effectively excluded an inlet component to any perimembranous defect.

From the patients studied it was evident that the larger the defect (synonymous with the greater the degree of posterior extension towards the crux) the more frequently were the atrioventricular valve septal leaflets attached at a common level to the base of the primum atrial septum (that is to the central fibrous body) throughout the extent of the defect (Fig. 4a). Pathological sectioning confirmed that this abnormal echocardiographic appearance results from an extension of the inlet component of the defect into the atrioventricular muscular septum either considerably reducing it in size (in small inlet perimembranous defects) or totally removing it (in large defects). This excavation of the atrioventricular muscular septum, by removing the structure that supports the oblique insertion of the atrioventricular valve rings to the septum, creates the common level of septal valve attachment. This was a constant feature of the perimem-


S
R
L
I
RA
TV
CFB
MV
LA
RV
LV
Tricuspid - mitral continuity in roof of defect
Left atrium
Left ventricle
2-D echocardiography of VSD
Perimembranous inlet septal defect
Precordial
Subcostal

(a) (b)

Fig. 4 *(a) A perimembranous inlet defect.* Upper panel: *a subcostal four chamber plane. The defect (arrowed) is bounded superiorly by central fibrous body and inferiorly by trabecular septum. Note the common level of insertion of the atrioventricular valve septal leaflets to central fibrous body.* Lower panels: *the equivalent specimens and diagram of a perimembranous inlet defect sectioned in a four chamber plane. RA, right atrium; LA, left atrium; RV, right ventricle; LV left ventricle; MV, mitral valve septal leaflet; TV, tricuspid valve septal leaflet; CFB, central fibrous body. (b) The echocardiographic pattern diagnostic of an inlet perimembranous defect.*

branous inlet defects studied.

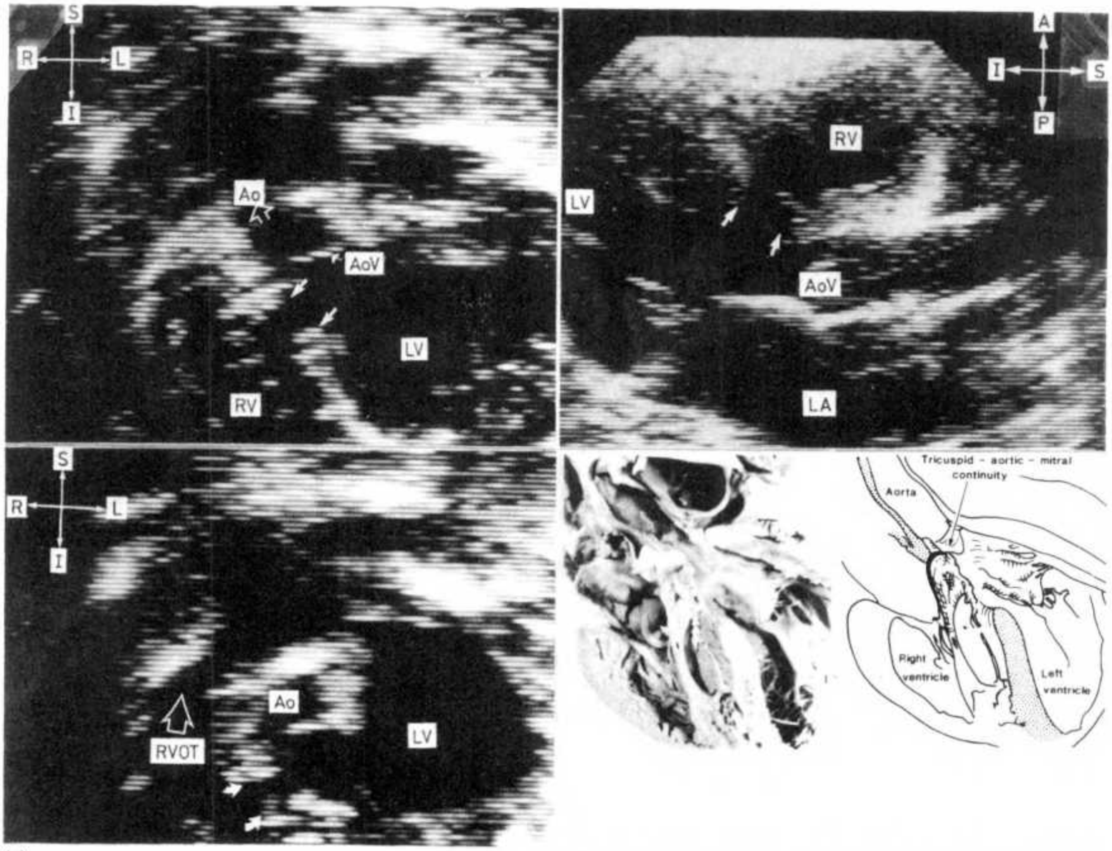
The two dimensional echocardiographic pattern and features diagnostic of a perimembranous inlet defect are illustrated in Fig. 4b.

(b) *Perimembranous outlet (subaortic or subpulmonary) defects* (84 patients)

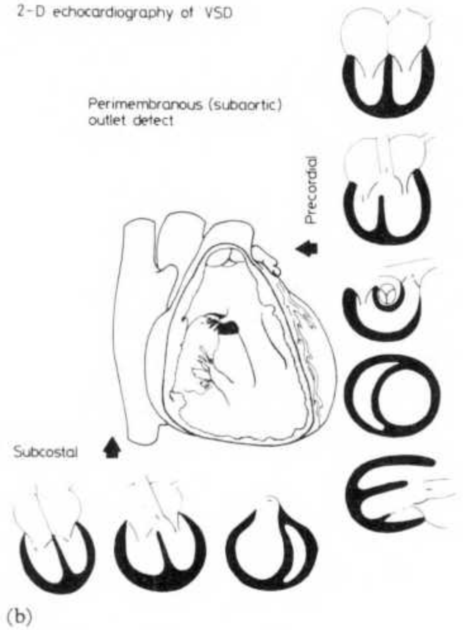
Eighty-four patients with such a defect were studied. In 83 of them, an area of membranous septal drop out was seen to extend anteriorly as the echo beam was swept anteriorly into the four chamber plus aortic root plane and then anteriorly across the posterior great vessel root from either the subcostal or precordial position. This echocardiographic feature confirmed the extension of the membranous defect into the outlet septum. (Where the posterior great vessel is the aorta then such defects are defined to be perimembranous (subaortic) outlet defects; where the posterior great vessel is the pulmonary artery then the defect is a perimembranous (subpulmonary) outlet defect.) The corresponding echocardiographic and morphological features of a perimembranous (subaortic) outlet defect are shown in Fig. 5a.

Large perimembranous outlet defects which excavate anteriorly beneath the whole posterior great vessel root were consistently visualised in the left ventricular long axis plane (Fig. 5a). Smaller defects did not extend into this plane. Perimembranous outlet defects were poorly visualised by short axis scanning.

In each of the 83 patients in whom a defect was



(a)


2-D echocardiography of VSD
Perimembranous (subaortic) outlet defect
Precordial
Subcostal

(b)

Fig. 5 *(a) A perimembranous outlet (subaortic defect) which extends into muscular outlet septum.* Upper left panel: *the defect (arrowed) visualised in a four chamber plus aortic root plane (membranous septum is absent)*. Upper right panel: *a precordial left ventricular long axis plane. The defect (arrowed) has excavated anteriorly beneath the whole aortic root.* Lower left panel: *a subcostal right ventricular outflow plane with the defect (arrowed) extending into the muscular outlet septum.* Lower right panel: *the corresponding specimen and diagram of a perimembranous outlet defect sectioned in a four chamber plus aortic root plane. RV, right ventricle; LV, left ventricle; Ao, aorta; AoV, aortic valve; LA, left atrium; RVOT, right ventricular outflow tract. (b) The echocardiographic pattern diagnostic of a perimembranous outlet defect.*

identified the roof of the defect was clearly seen to be formed by the valve ring of the posterior great vessel and not by a downward projection of muscular outlet septum. The floor of the defect was seen to be part of the trabecular septum. These features allowed perimembranous outlet defects to be accurately classified with great consistency.

The two dimensional echocardiographic pattern and features diagnostic of a perimembranous (subaortic) outlet defect are illustrated in Fig. 5b.

(c) *Perimembranous trabecular defects* (19 patients)
Small membranous defects which extended inferiorly into the trabecular septum were only visualised at the most posterior aspect of the four chamber plus aortic root plane using either the subcostal or precordial view. They could also be recorded in a short axis scan but this was rare (three patients). Such defects did not extend anteriorly below the aortic valve for any significant distance. They were never visualised in the left ventricular long axis plane.

In the normal heart two dimensional echocardiography cannot determine the precise junction of membranous and trabecular septa. Thus, in theory it should prove difficult to identify when the trabecular septum becomes involved in a membranous defect. This is borne out in practice. Correlating echocardiographic with morphological findings, however, suggested two non-specific features that indicate trabecular septal involvement: (i) a blunt upper margin of the interventricular septum which forms the floor of the defect and (ii) where a membranous defect extends apically for more than half the aortic root diameter.

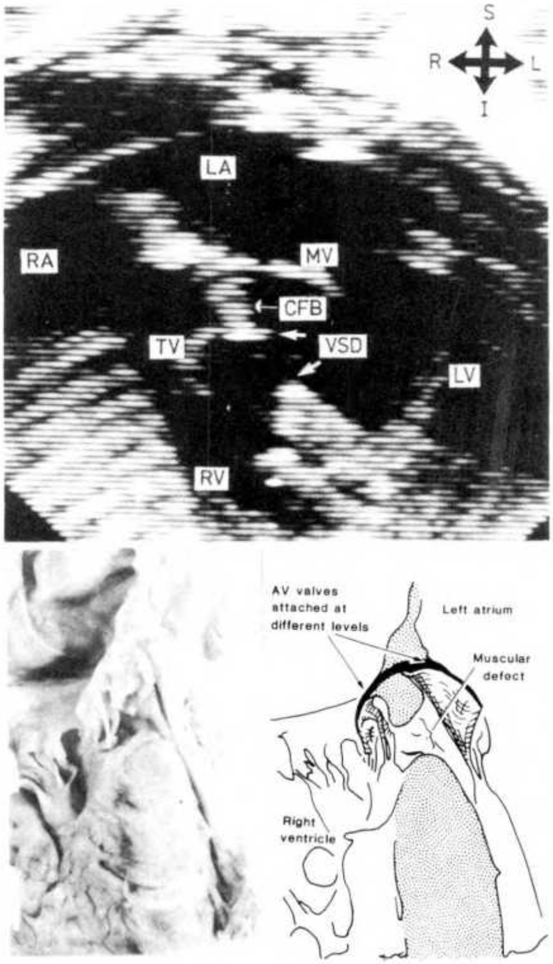
Nineteen patients with perimembranous trabecular defects were studied. The defect was correctly identified in 16 patients. In the three patients previously described, the ventricular septum appeared intact in every echocardiographic plane.

(d) *Large perimembranous defects* (39 patients)
Morphologically these defects all extend from the membranous septum into the inlet, trabecular, and outlet septa. These defects were correctly identified in each of the 39 patients studied and were the largest defects recorded during the entire series. It proved impossible in each case to determine which of the surrounding areas was predominantly involved and thus subdivision of these defects was not practical. The individual features of each component of such a defect were consistently visualised in the appropriate echocardiographic planes.

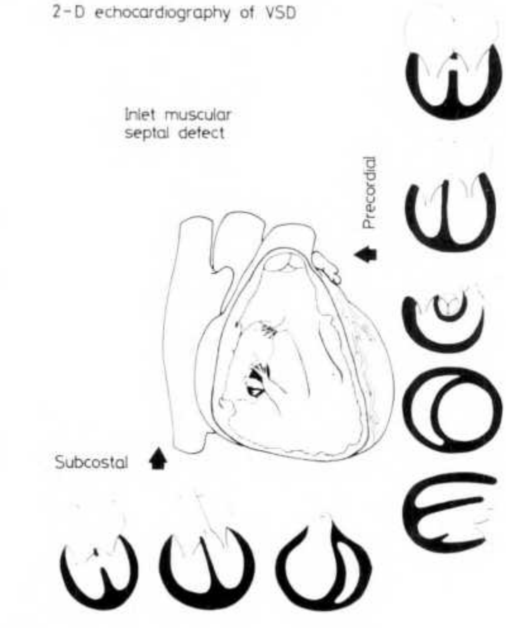
MUSCULAR DEFECTS (71 patients)
As indicated, the morphological feature diagnostic of a muscular defect is that it is entirely surrounded by muscle and is not directly bordered by either central fibrous body or by an arterial or atrioventricular valve. The corresponding two dimensional echocardiographic features were used to identify muscular defects. Seventy-one patients with muscular defects were studied. Defects in the inlet and outlet muscular septa were consistently identified but trabecular defects were inconsistently identified. The differing echocardiographic patterns diagnostic of each type of defect are described below.

(a) *Inlet muscular defects* (18 patients)
Inlet muscular defects were consistently visualised when scanning through the four chamber plane (either subcostal or precordial) in each of the 18 patients studied. These defects were not visualised in any other plane. They always appeared larger when visualised from the subcostal approach because this view profiles the inlet septum without foreshortening it. The following echocardiographic features distinguished these defects from perimembranous inlet defects: (i) The downwards projection of a bar of muscle from the atrioventricular junction which formed the upper muscular rim of the defect and which separated the defect from the central fibrous body, (ii) a normal pattern of septal atrioventricular valve insertion (inlet muscular defects do not excavate into the atrioventricular muscular septum in contrast to inlet perimembranous defects), and (iii) when scanning anteriorly from the four chamber plane across the area of the membranous septum the muscular inlet defect is lost and the normal continuity of central fibrous body, aortic root, and membranous septum remains intact. The two dimensional echocardiographic and morphological features of a muscular inlet defect are illustrated in Fig. 6a and b.

(b) *Outlet muscular defects* (six patients)
Six defects with entirely muscular rims were located in the outlet septum by two dimensional echocardiography. The full extent of these defects was only visualised from the subcostal position when scanning anteriorly from the four chamber plus aortic root plane to the right ventricular outflow plane. Morphological sectioning of the normal heart confirmed that this is the only echocardiographic approach which will accurately profile both the subaortic and subpulmonary portions of the outlet septum. In all six patients the defect was seen to be located predominantly in the anterior aspect of the right ventricular outflow plane in a subpulmonary position but separated from the pulmonary valve by a long muscular infundibulum (Fig. 7a). In four of these patients the defect extended a short distance posteriorly into the four chamber plus aortic root plane, indicating involvement of the muscular septum below the aortic



(a)



(b)

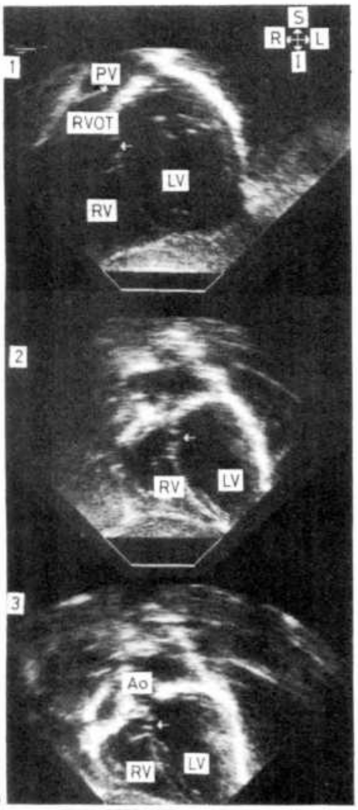
Fig. 6 *(a) An inlet muscular defect shows the following.* Upper panel: *the defect (between arrows) visualised in a four chamber plane. Note the atrioventricular valve septal leaflets are well separated by the intact atrioventricular septum. A muscle bar projects downwards from central fibrous body to roof the defect.* Lower panel: *the corresponding pathological specimen and diagram of an inlet muscular defect. RA, right atrium; LA, left atrium; RV, right ventricle; LV, left ventricle; TV, tricuspid valve septal leaflet; MV, mitral valve septal leaflet; CFB, central fibrous body. (b) The echocardiographic pattern diagnostic of an inlet muscular defect.*

root. In each case the defect was separated from the aortic root by a bar of muscle. No defect extended posteriorly to the level of the membranous septum. Fig. 7c shows the corresponding morphological features of such a defect. The two dimensional echocardiographic features and pattern diagnostic of an outlet muscular defect are illustrated in Fig. 7a and b.

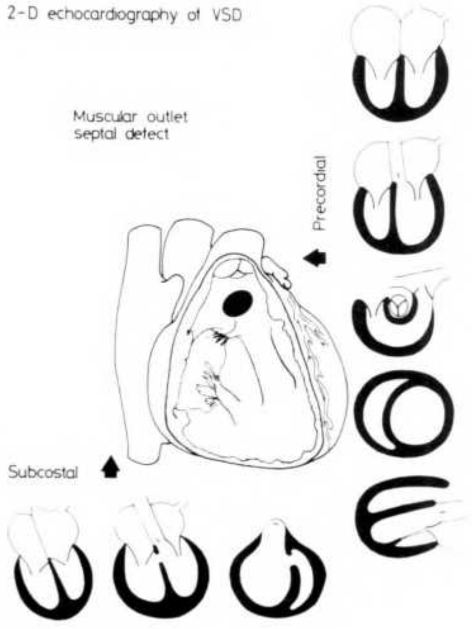
(c) *Trabecular muscular defects* (47 patients)
Defects in the trabecular portion of the muscular septum were inconsistently identified by two dimensional echocardiography.

Single trabecular septal defects (43 patients) could be recognised. These defects were best visualised on short axis scanning (either precordial or subcostal). They could be clearly located in either the anterior or posterior trabecular septum and never involved the membranous septum (Fig. 8a and b). Where the defect was recognised on short axis scanning it was usually also identified on four chamber or long axis scanning but this was not always the case. Some surprisingly large single trabecular defects ($Qp:Qs>1{\cdot}5:1$) were missed, however, on two dimensional scanning. Small single trabecular defects ($Qp:Qs<1{\cdot}5:1$) were never identified in this series.

Multiple small trabecular defects (four patients) (the so-called Swiss cheese defect) were not identified in this study. In each of the four patients studied the septum appeared intact in every plane recorded. The problems encountered in defining multiple small trabecular defects (and single small trabecular defects) were explained by examining their morphology. Fig. 9a shows a heart with multiple small trabecular defects easily visualised when viewed from the right ventricular surface of the septum. Fig. 9b shows the



(a)



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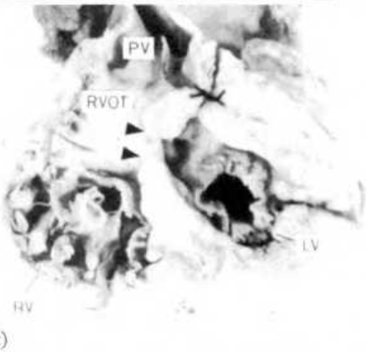


(c)

Fig. 7 *(a) An outlet muscular defect (extending posteriorly to involve trabecular septum). A composite slide of three still frames from a subcostal right ventricular outflow → four chamber plus aortic root scan, illustrating the advantage of the scan technique. The defect (arrowed) is initially visualised in frame 1 lying within the muscular outlet septum and separated from the pulmonary valve by infundibular septum. In frame 2, an intermediate plane, the defect remains bounded by muscle. In frame 3 (four chamber plus aortic root plane) the most posterior extent of the defect lies within trabecular septum below an intact membranous septum. PV, pulmonary valve; RVOT, right ventricular outflow tract; RV, right ventricle; LV, left ventricle; Ao, aorta. (b) The echocardiographic pattern diagnostic of a muscular outlet defect. (c) A pathological specimen of a muscular outlet defect (defect arrowed) sectioned in a subcostal right ventricular outflow plane. Note how precisely two dimensional echocardiography (Fig. 7a) defines the morphological features. PV pulmonary valve; RVOT, right ventricular outflow tract; RV, right ventricle; LV, left ventricle.*

same heart sectioned in the four chamber echocardiographic plane. Note that in this view the septum will appear grossly intact to the echocardiographer. The small trabecular defects are seen to burrow through the septal mass in a spiral or oblique fashion. Such defects do not produce a complete echocardiographic window across the width of the septum and thus the septum will always appear intact to the echo beam. Sectioning hearts with similar defects in a series of echocardiographic planes confirmed the validity of this explanation. From these findings it seems unlikely that two dimensional echocardiography can reliably identify multiple trabecular or small single trabecular defects.

DOUBLY COMMITTED SUBARTERIAL DEFECTS (24 patients)

The morphological feature which defines a doubly committed subarterial defect is that it is roofed by conjoint aortic and pulmonary valve rings that lie at the same level. These features were well defined by two dimensional echocardiography (Fig. 10a and b). In each of the patients the ventricular septum appeared intact throughout the four chamber plane. When scanning anteriorly to the aortic root, however, both aortic and pulmonary valves were simultane-

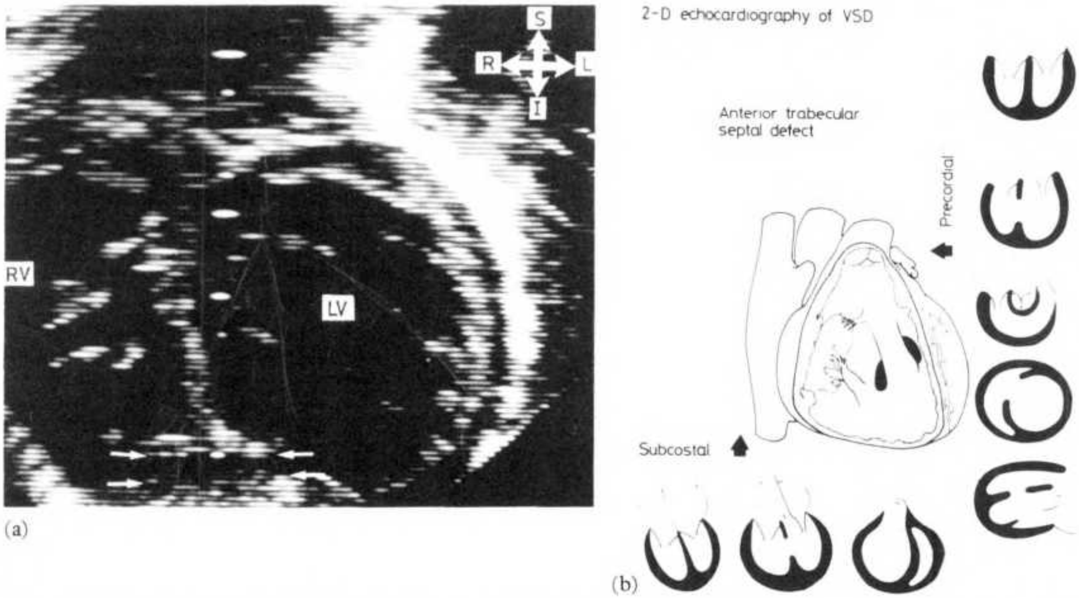

S
R
L
I
RV
LV
(a)
2-D echocardiography of VSD
Anterior trabecular septal defect
Precordial
Subcostal
(b)

Fig. 8 *(a) An anterior trabecular defect (between arrows) visualised in a precordial short axis section. (b) The echocardiographic pattern diagnostic of a large anterior trabecular defect.*

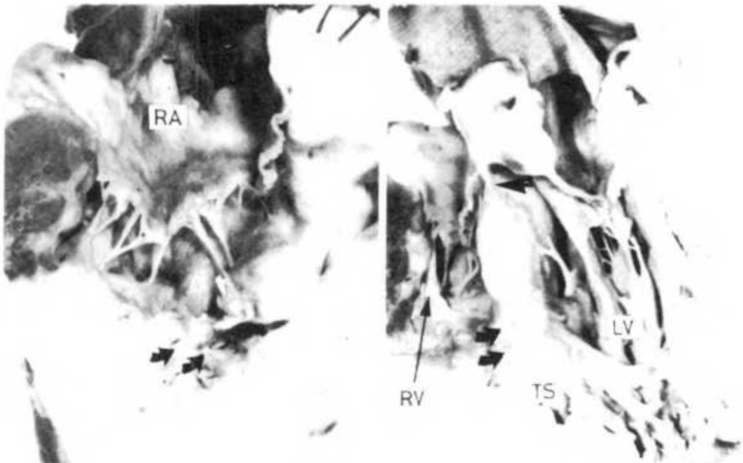
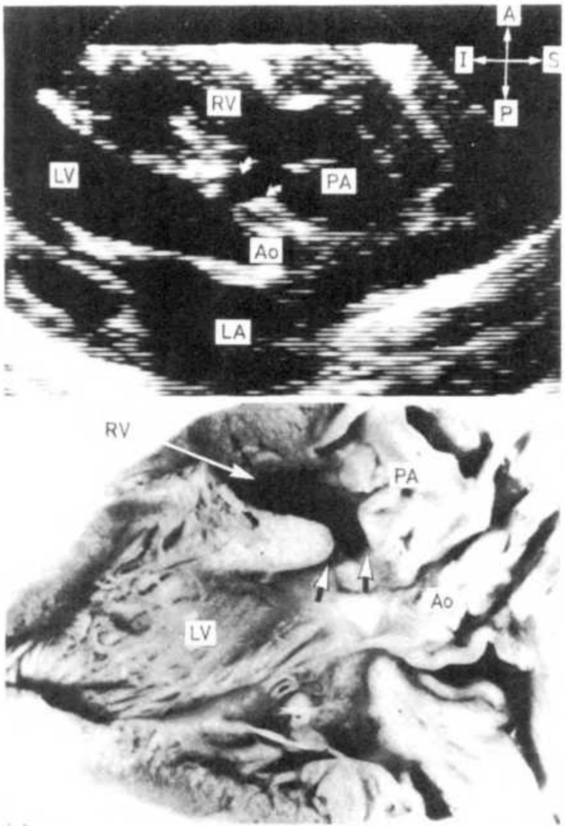


Fig. 9 *A pathological specimen showing multiple small trabecular defects. (a) The right ventricular septal surface with the area of multiple defects arrowed. (b) The same heart sectioned in a four chamber plane. Note the defects (small arrows) burrow through the septum in an oblique manner. There is no discrete area where the whole septal width is absent. The septum will appear intact on two dimensional echocardiography. RA, right atrium; RV, right ventricle; LV, left ventricle; TS, trabecular septum (large arrow indicates intact membranous septum).*

ously visualised lying at the same level, in the same echocardiographic plane and in a side-by-side relation. These conjoint arterial valves roofed a large ventricular septal defect whose inferior margin was formed by the crest of the trabecular septum. In nine patients this subarterial defect extended posteriorly to involve the area of the membranous septum. In the remaining 15 patients the membranous septum appeared intact and the posterior rim of the defect was clearly formed by muscle. Thus, two dimensional echocardiography could clearly define doubly committed subarterial defects and subdivide them into two types: (i) those that involve the membranous septum and (ii) those separated from it by a muscle bar.

Doubly committed subarterial defects were consistently recognised using a scan through the four chamber plus aortic root plane (either subcostal or precordial) (Table). The area of septal drop out was



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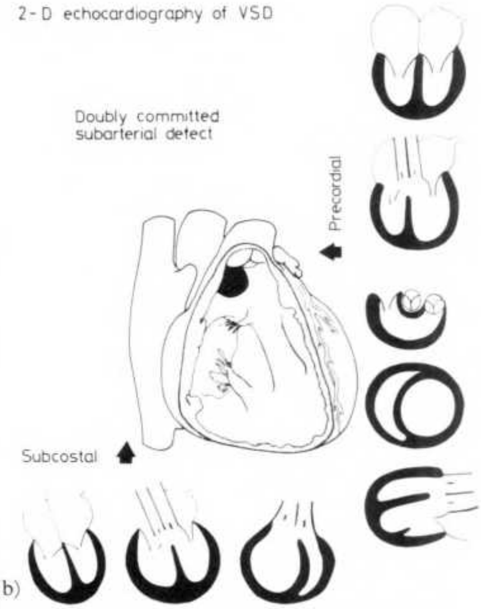
2-D echocardiography of VSD
Doubly committed subarterial defect
Precordial
Subcostal

(b)

Fig. 10 *(a) A doubly committed subarterial defect.* Upper panel: *a left ventricular long axis plane. Note the conjoint aortic and pulmonary valve rings which roof the defect (arrowed).* Lower panel: *the corresponding pathological specimen sectioned in a left ventricular long axis plane. Ao, aorta; PA, pulmonary artery; LV, left ventricle; RV, right ventricle. (b) The echocardiographic pattern diagnostic of a doubly committed subarterial defect.*

consistently visualised in a subaortic position on precordial long axis scanning, but this view did not always clearly show conjoint aortic and pulmonary valve rings. These defects were not well categorised by short axis scanning.

Discussion

Although the ventricular septum is formed from a number of morphologically distinct subunits it appears as a virtually homogeneous structure on two dimensional echocardiography. The septum may vary in width in different echocardiographic planes but little distinction can be made between individual subunits. The only portion that can be consistently differentiated in the normal heart is the interventricular portion of the membranous septum. Thus, precise localisation of defects within the ventricular septum will only be possible if we appreciate which septal subunits form the composite septal structure visualised in each echocardiographic plane.

Where a defect is identified by an area of persistent septal "drop out" it can be determined through which echocardiographic planes this area extends and where it appears within the septum in each plane. This information will determine the position and extent of a septal defect but will not accurately classify it. How then should we best classify ventricular septal defects using the information which two dimensional echocardiography can provide?

The increased resolution of two dimensional systems now allows specific features of cardiac morphology to be imaged in detail. The aortic root and valve, the central fibrous body (that is the area enclosed by the fibrous annuli of the tricuspid, mitral, and aortic valves and so comprised of the right fibrous trigone and the atrioventricular membranous and muscular septa), the interventricular membranous septum, the infundibular septum, and the pulmonary valve are all readily identified. With this degree of resolution it is now appropriate to base any echocardiographic classification on the identification of all the structures that form the rim of a defect. Thus the morphological classification adopted prospectively was that initially proposed by Moulaert[6] which subdivided defects on precisely this basis. This classification was subsequently modified to a minor degree during the investigation in view of our findings (Fig. 2).

To determine if this method of classification was both practical and reliable we reviewed 280 patients with a ventricular septal defect. Using a multiplane scanning technique to construct an approximate three dimensional model of the heart we identified a defect in 252 patients. In each case the structures forming the margins of a defect were readily identified, thus allowing accurate classification into one of three main groups (Fig. 2). The further subdivision of these main groups, based on which septal subunit is predominantly involved, was determined by the echocardiographic planes in which the defect was visualised (for example a defect roofed in part by the central fibrous body but otherwise surrounded by muscle is a perimembranous defect; where such a defect is only visualised in a four chamber plane which profiles the inlet septum it is subclassified as a perimembranous inlet defect). Defects frequently extend across the boundaries of individual septal components, however, and this information should be included in any description of a defect (for example the majority of muscular outlet defects studied were not restricted to the right ventricular outflow plane but were traced posteroinferiorly into the four chamber plus aortic root plane where they burrowed into the trabecular septum. Such a defect should therefore be described as a muscular outlet defect which extends posteroinferiorly into the trabecular septum). In our experience, two dimensional echocardiography accurately subdivided septal defects within each of the three main groups on the basis of which septal subunit was predominantly involved, and in addition accurately identified any extension into an adjoining septal subunit.

Different defects were identified with different degrees of accuracy (Table). Perimembranous inlet and outlet defects, doubly committed subarterial defects, and inlet and outlet defects of the muscular septum were all identified with remarkable consistency, whereas defects of the trabecular septum were identified with varying degrees of success. Multiple small (Swiss cheese) trabecular defects were not identified in this series. Single trabecular defects were inconsistently visualised, with some correlation existing between defect size and defect recognition. When divided into two groups on the basis of intracardiac shunting (small defects with a $Qp:Qs<1{\cdot}5:1$ and large defects with a $Qp:Qs>1{\cdot}5:1$, Table) it was clear that small defects were not visualised at all compared with 72% recognition of large defects. Some surprisingly large trabecular defects, however, were not visualised.

The above findings show broad agreement with the results of previously published series.[2 3] Both these series, however, have confined their investigation to the identification of septal defects in infants and have restricted their echocardiographic approach to the subcostal window. Though a subcostal approach will yield more information when compared with a precordial approach (the muscular outlet septum is only profiled from the subcostal window) it can be extremely difficult to record in older children and adolescents. In these cases a precordial approach may be the only means of visualising a defect. Information can be gained from the precordial approach, however, which is not readily obtainable from the subcostal window (for example the anterior extension of a perimembranous subaortic defect beneath the whole aortic root was clearly visualised only in a left ventricular long axis plane; similarly, anterior trabecular defects were best visualised by precordial short axis scanning, being frequently missed from the subcostal approach).

We suggest that the composite approach adopted in this study in which the heart is visualised from both the subcostal and precordial window and where a scanning technique is used to determine the extent of any defect will provide the maximum amount of information. It will accurately identify and classify the majority of ventricular septal defects in infants, children, and adolescents, and thus offers considerable advantages over previously described echocardiographic techniques for studying the ventricular septum.

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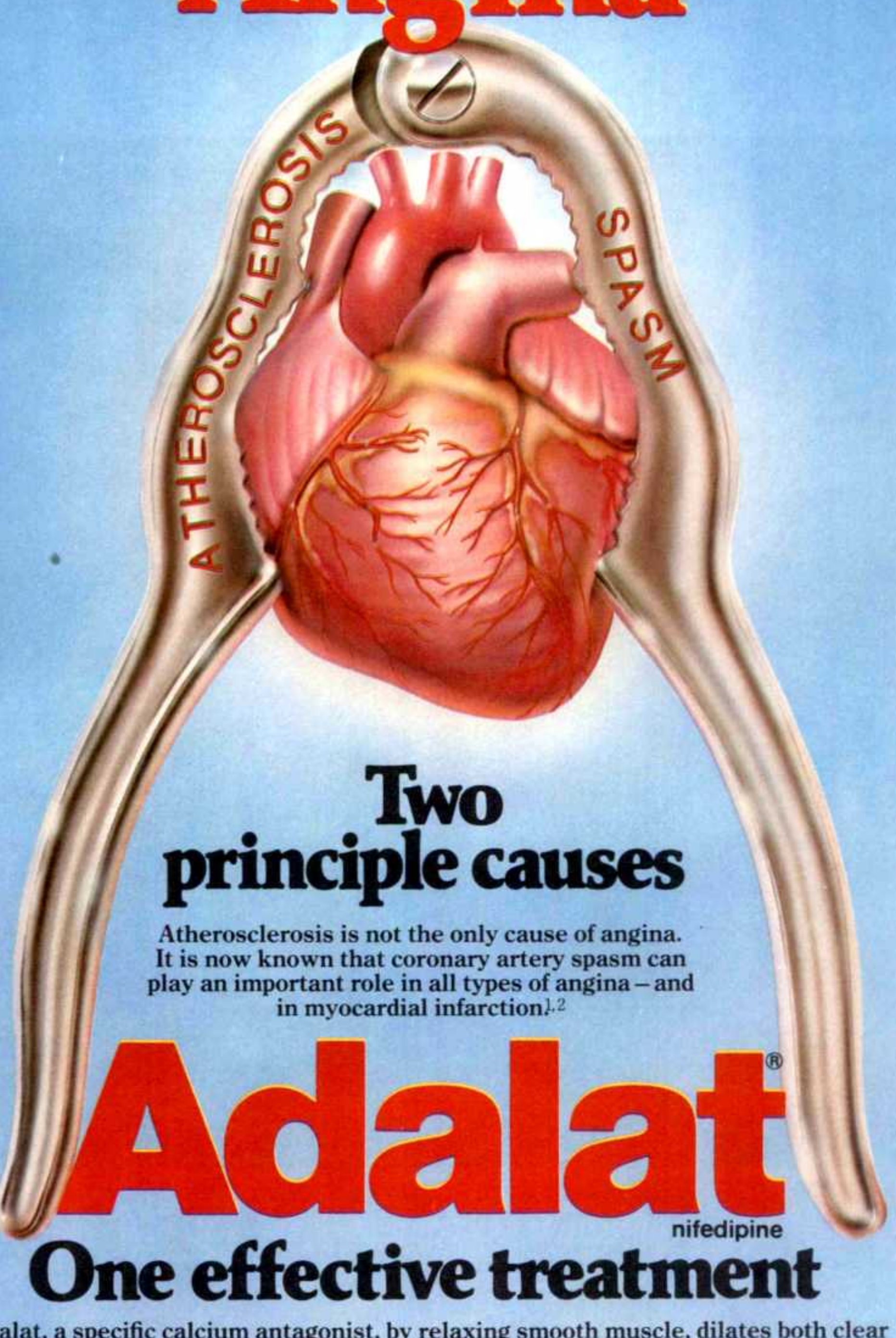
Angina



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References 1. *Brit Med J* 1979; **1** : 969-70 2. *Amer J Cardiol* 1979; **44** : 788-92 3. *Eur Heart J* 1980; **1** (Suppl B) : 71-85 4. *J Roy Soc Med* 1980; **73** : 570-5 5. 3rd International Adalat Symposium. Amsterdam – Oxford: Excerpta Medica, 1976: 303-5 6. *New England J Med* 1980: **302** : 1269-73 7. *Br Med J* 1980; **281** : 184-3

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Br Heart J 1982; 47: 329–36

Recognition of imperforate atrioventricular valves by two dimensional echocardiography

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SUMMARY The majority of hearts in which selective right or left atrial angiography shows no direct communication between one atrium and a ventricular chamber are considered to be examples of atresia of the right or left atrioventricular valves. Most patients presenting with the clinical features of tricuspid atresia have an absent right atrioventricular connection, while those with features of mitral atresia and a normal aortic root frequently have an absent left atrioventricular connection. By studying 67 patients using two dimensional echocardiography we have identified 12 in whom there was an imperforate atrioventricular valve and not an absent atrioventricular connection. Thus, in 44 hearts with the angiographic features of tricuspid atresia, 36 had absence of the right atrioventricular connection and six had an imperforate right atrioventricular valve. In the latter, four were examples of atrioventricular concordance and two were univentricular hearts of left ventricular morphology in which the mode of atrioventricular connection was through one perforate and one imperforate valve. Similarly, 17 out of 23 cases of mitral atresia had absence of the left atrioventricular connection. The remaining six had an imperforate left atrioventricular valve which was associated with atrioventricular concordance in two patients and with double inlet univentricular hearts in four patients.

The majority of hearts with what is generally termed "tricuspid atresia" are examples of absent right atrioventricular connection.[1–3] The cardinal anatomical feature is the absence of any potential communication between the floor of the right atrium and the ventricular mass, sulcus tissue interposing between them. In some cases, however, a similar clinical picture may emerge when there is an imperforate right atrioventricular valve.[1–4] These hearts may be examples of atrioventricular concordance, atrioventricular discordance, or univentricular hearts. Similarly, isolated mitral atresia may be an example of either absent left atrioventricular connection or imperforate left atrioventricular valve. Mitral atresia is commonly associated with aortic valve atresia or severe aortic stenosis, and pronounced hypoplasia of the ascending aorta. This group of abnormalities is often associated with an imperforate mitral valve and is incompatible with life beyond the neonatal period.[5] In mitral atresia with a normal aortic root, however, which carries a better prognosis, the type of atrioventricular connection is most commonly absent left connection.

The hallmark of an imperforate valve is that it provides potential communication between an atrium and a ventricle. It exists as fused valve leaflets usually possessing their own hypoplastic tensor apparatus. The presence of an imperforate valve may have important surgical implications. For example, in hearts with atrial situs solitus and atrioventricular concordance, a valvotomy of an imperforate tricuspid valve may perhaps be preferable to a Fontan procedure.

In the past, diagnosis of this abnormality has been impossible clinically, and extremely difficult on angiography because of the similarities in the appearances of hearts with an absent atrioventricular connection. M-mode echocardiography alone is of some value in the demonstration of an imperforate valve,[6] but two dimensional echocardiography, by providing detailed visualisation of the atrioventricular junction, would be expected to identify such an abnormality. It is for this reason that our study was undertaken.

Patients and methods

Forty-four patients with angiographic features of "tricuspid atresia" and 23 with features of "mitral

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atresia" (with a normal aortic root and ascending aorta) were studied by echocardiography. Their ages ranged from 1 day to 14 years and in each case absence of anterograde flow from an atrium had been demonstrated by angiography. Two dimensional echocardiograms were performed using an Advanced Technology Laboratories wide angled mechanical sector scanner. The examination was carried out in such a way as to show both the type and mode of atrioventricular connection using selected tomographic views of the heart.[7] In the majority of cases, echocardiograms were recorded on a video display system which allowed repeated examination of the original real time images. Those hearts possessing an imperforate right or left atrioventricular valve were selected for inclusion in the study. Those with absent right or left atrioventricular connection were excluded.

Results

Two dimensional echocardiography showed the precise type and mode of atrioventricular connection in 65 of the 67 patients with tricuspid or mitral atresia. In 12 cases there was unequivocal evidence of an imperforate valve and these hearts are those included in the present study. Of the remainder, 53 hearts were considered to be examples of either absent left or absent right atrioventricular connection, though in eight cases the distinction between absent connection and thickened imperforate valve could not be made with certainty. Unsatisfactory echocardiograms were recorded in two patients.

IMPERFORATE RIGHT ATRIOVENTRICULAR VALVE (Table 1)

(a) *With atrioventricular concordance*

All the four hearts with atrioventricular concordance were characterised by having the right atrium separated from a hypoplastic right ventricle by an imperforate membrane (Fig. 1). The tensor apparatus of the valve could be seen only in two cases. In each of the four patients, the recognition of the small right sided hypoplastic right ventricle as one of right ventricular morphology was dependent upon identifying the septal portion of the imperforate valve dividing the ventricular septum into atrioventricular and interventricular parts (Fig. 1).

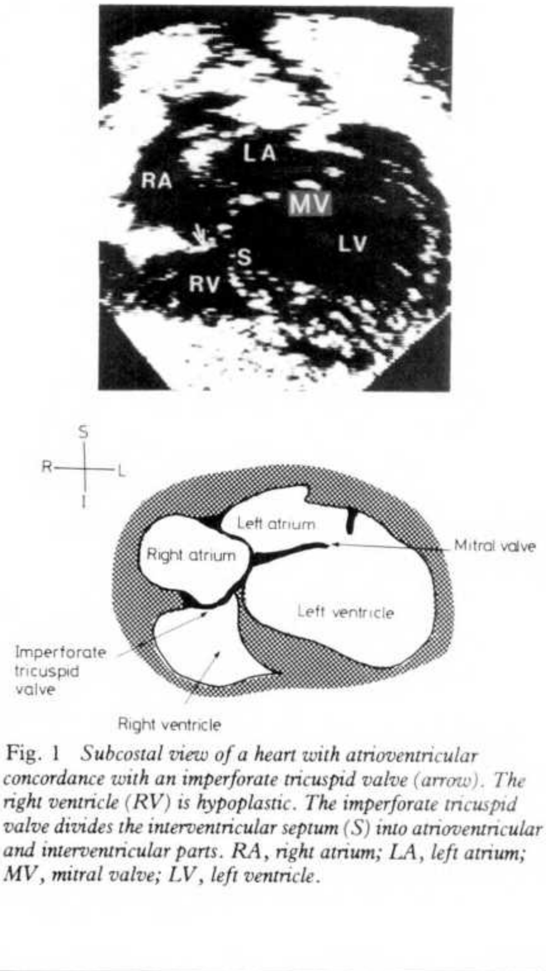

Fig. 1 *Subcostal view of a heart with atrioventricular concordance with an imperforate tricuspid valve (arrow). The right ventricle (RV) is hypoplastic. The imperforate tricuspid valve divides the interventricular septum (S) into atrioventricular and interventricular parts. RA, right atrium; LA, left atrium; MV, mitral valve; LV, left ventricle.*

Table 1 *Imperforate right atrioventricular valve*

Case No.	*Atrial situs*	*Type of atrioventricular connection*	*Ventriculoarterial connection*	*Associated abnormalities*
1	Solitus	Concordant	Concordant	Atrial septal defect, pulmonary valve atresia
2	Solitus	Concordant	Concordant	Patent foramen ovale, pulmonary atresia
3	Solitus	Concordant	Concordant	Patent foramen ovale, ventricular septal defect, severe subpulmonary stenosis
4	Solitus	Concordant	Concordant	Atrial septal defect, ventricular septal defect, pulmonary atresia
5	Solitus	Double inlet ventricle*	Concordant	Patent foramen ovale, pulmonary atresia
6	Solitus	Double inlet ventricle*	Discordant	Atrial septal defect, pulmonary artery banding

*Univentricular heart of left ventricular type.

(b) *With double inlet ventricle*

In the two univentricular hearts with an imperforate right atrioventricular valve, the mode of atrioventricular connection was by one perforate and one imperforate valve (Fig. 2). An imperforate valve was seen as a thin membrane between the right atrium and the main left ventricular chamber, but in only one case was there unequivocal demonstration of tensor apparatus. The characteristic feature of these hearts was that the atrioventricular connections were posterior to the septum present in the ventricular mass; hence they were univentricular hearts of left ventricular morphology.

IMPERFORATE LEFT ATRIOVENTRICULAR VALVE (Table 2)

(a) *With atrioventricular concordance*

Two hearts with atrioventricular concordance had an imperforate membrane between the left atrium and a hypoplastic left ventricle. Tensor apparatus was identified in one of these (Fig. 3). The recognition of the small left sided ventricle as one of left ventricular morphology was based upon identifying its smooth trabecular pattern (Fig. 4). In both cases the septal leaflet of the perforate right atrioventricular valve divided the ventricular septum into atrioventricular and interventricular parts, confirming that the large right sided ventricle was of right ventricular morphology (Fig. 4).

(b) *With double inlet ventricle*

In each of the four univentricular hearts, the mode of atrioventricular connection was through a perforate right and an imperforate left atrioventricular valve. Rudimentary tensor apparatus was identified in two. The characteristic feature of the two univentricular hearts of right ventricular morphology was that the atrioventricular junction was anterior to the septum present in the ventricular mass, whereas in the two

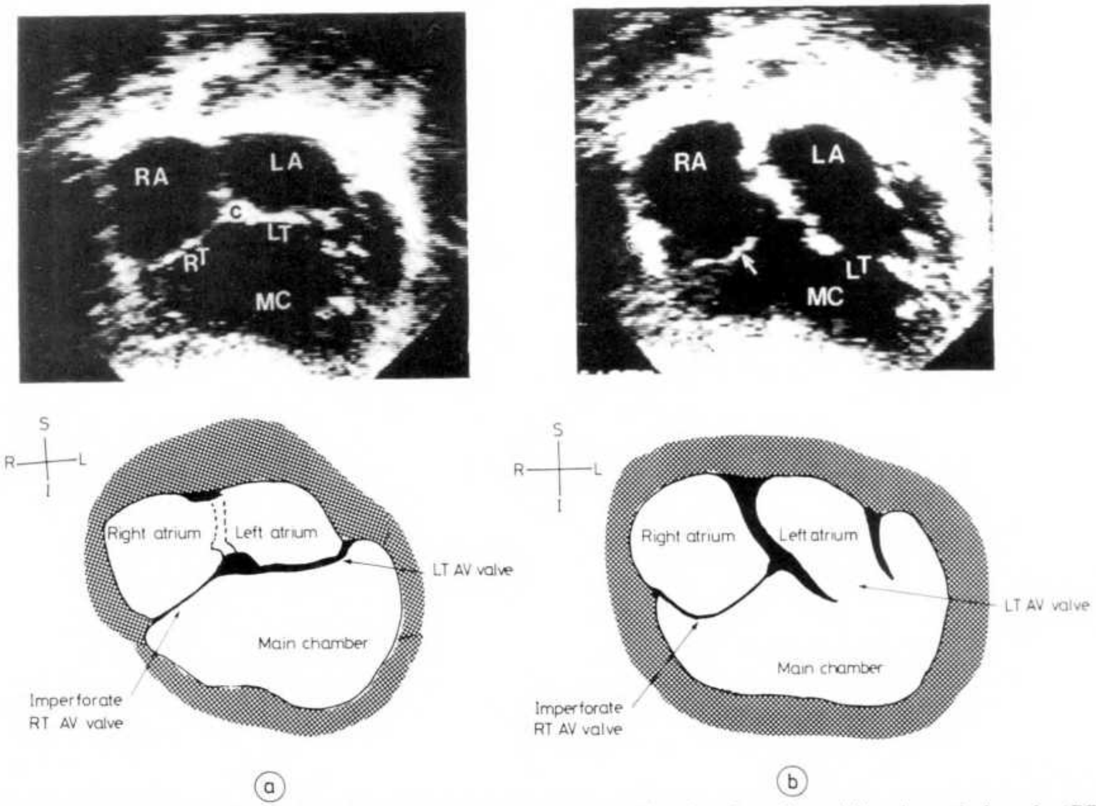

Fig. 2 *(a) Apical view of double inlet univentricular heart taken in systole. There is an imperforate right atrioventricular valve (RT) and the left atrioventricular valve (LT) is closed. RA, right atrium; LA, left atrium; MC, main chamber; C, central fibrous body. (b) Apical view of double inlet univentricular heart taken in diastole. The imperforate right atrioventricular valve is shown by an arrow and the left atrioventricular valve (LT) is open.*

Table 2 *Imperforate left atrioventricular valve*

Case No.	*Atrial situs*	*Type of atrioventricular connection*	*Ventriculoarterial connection*	*Associated abnormalities*
7	Solitus	Concordant	Concordant	Atrial septal defect, ventricular septal defect
8	Solitus	Concordant	Concordant	Patent foramen ovale, ventricular septal defect
9	Solitus	Double inlet ventricle*	Concordant	Atrial septal defect, coarctation, subpulmonary stenosis
10	Solitus	Double inlet ventricle*	Concordant	Atrial septal defect, cardiomyopathy, subaortic stenosis
11	Solitus	Double inlet ventricle†	Double outlet ventricle	Atrial septal defect, pulmonary atresia, partial anomalous pulmonary venous drainage
12	Solitus	Double inlet ventricle†	Double outlet ventricle	Atrial septal defect, subpulmonary stenosis

*Univentricular heart of right ventricular type.
†Univentricular heart of indeterminate type.

univentricular hearts of indeterminate morphology it was not possible to identify a second chamber within the ventricular mass.

PROBLEM CASES

In eight cases, five with tricuspid atresia and three with mitral atresia, the distinction between absent atrioventricular connection and an imperforate valve was difficult. In each case a thick echo, interposed between the floor of the atria and ventricle, could have been interpreted as either sulcus tissue or a thick imperforate valve (Fig. 5). Unless we have demonstrated a thin membrane or the tensor apparatus we have considered the atrioventricular connection to be absent.

Discussion

The atrioventricular junction is that part of the heart where the atria connect to the ventricles. In the normal heart it is made up of two fibrous annuli which also support the leaflets of the atrioventricular valves. It is our practice to define the *type* of atrioventricular connection as the way the atria are connected, via the fibrous annuli, to the ventricles. We refer to the morphology of the valves which guard the atrioventricular junction as the *mode* of atrioventricular connection.[2,3]

In hearts with two ventricles the type of atrioventricular connection may be concordant, discordant, or ambiguous, the latter being applicable when the atria themselves are isomeric.[8] In a univentricular heart, which we define as any heart in which only one ventricular chamber possesses an atrioventricular connection or connections, the type of atrioventricular connection may be double inlet (both atria connecting to one ventricle), absent right, or absent left connection.[9,10] When both atria have a direct connection to the ventricular mass, the mode of atrioventricular connection may be via two discrete valves or by a common valve. When two valves are present, one of them may be imperforate or may override or straddle a septum.

In hearts with an imperforate right atrioventricular valve, the clinical presentation may be identical to classical tricuspid atresia (absent right connection) and similarly an imperforate left atrioventricular valve can be indistinguishable, from the clinical standpoint, from isolated absence of the left atrioventricular connection.[11] This is true if the imperforate valve is associated with concordant or discordant atrioventricular connections or with double inlet univentricular heart.

Imperforate right atrioventricular valves have been described by several authors, albeit in most instances briefly.[1,4,12–14] There have been two descriptions associated with Ebstein's anomaly.[15,16] The features of an imperforate left atrioventricular valve have been mentioned by some authors without complete descriptions.[11,12] In contrast, others have failed to acknowledge the distinction between an absent connection and an imperforate valve in detailed accounts of tricuspid atresia, mitral atresia, or univentricular hearts.[17–19] We have described the two dimensional echocardiographic features of imperforate valves in 12 patients and have included not only hearts with atrioventricular concordance but also those with double inlet univentricular hearts. There appear to be no detailed published accounts of the latter. It is conceivable that hearts exist with an imperforate left or right atrioventricular valve in which the type of atrioventricular connection is discordant but we have not discovered any.

In the past, the diagnosis of an imperforate valve was of little clinical significance and could be made with certainty only at necropsy. We have previously described the two dimensional echocardiographic features of univentricular hearts, including those with absent right or left atrioventricular connections.[9] This

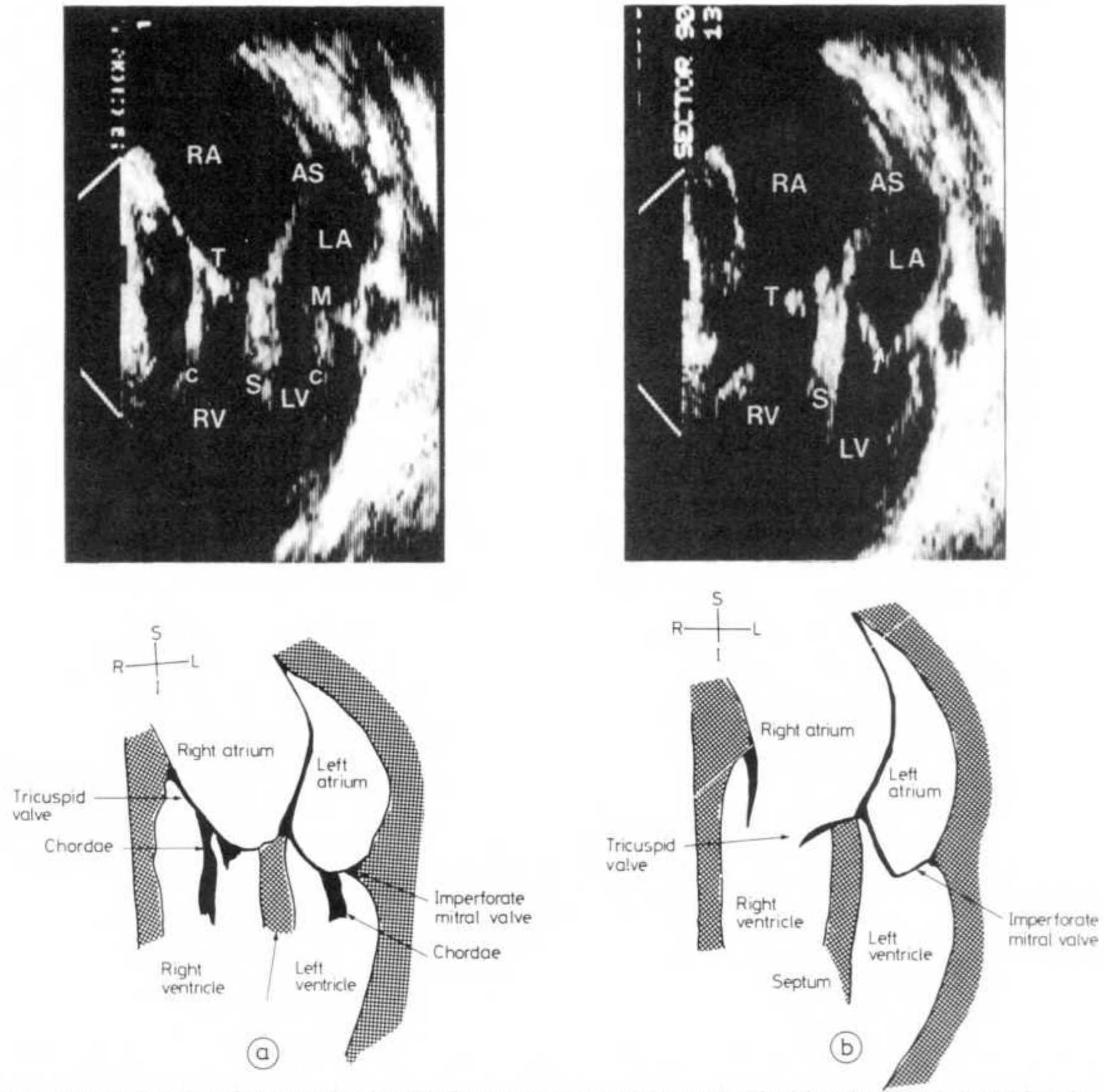

Fig. 3 *(a) Subcostal view of a heart with atrioventricular concordance recorded in systole. The right atrium (RA) is divided from the small left atrium (LA) by the atrial septum (AS). The tensor apparatus (C) of the tricuspid valve (T) is clearly seen in the right ventricle (RV). The tensor apparatus (C) of the imperforate mitral valve (M) is clearly seen in the left ventricle (LV). S, interventricular septum. (b) Subcostal view of the same heart recorded during diastole. The tricuspid valve (T) is open. The mitral valve (arrow) remains closed because it is imperforate.*

study has shown that two dimensional echocardiography permits accurate assessment of the atrioventricular junction when the mode of connection is through one perforate and one imperforate valve. Moreover, hearts with atrioventricular concordance or discordance can be distinguished from univentricular hearts with double inlet connection. The cornerstone of the diagnosis of an imperforate valve is the identification of a thin mobile membrane between an atrium and a ventricle and the recognition of the tensor apparatus of the valve. In the majority of cases the tensor apparatus is hypoplastic and therefore its delineation by echocardiography is not always possible. Indeed it may not be discovered at necropsy. In some instances the imperforate membrane may be thickened, then, without the demonstration of the tensor apparatus, an

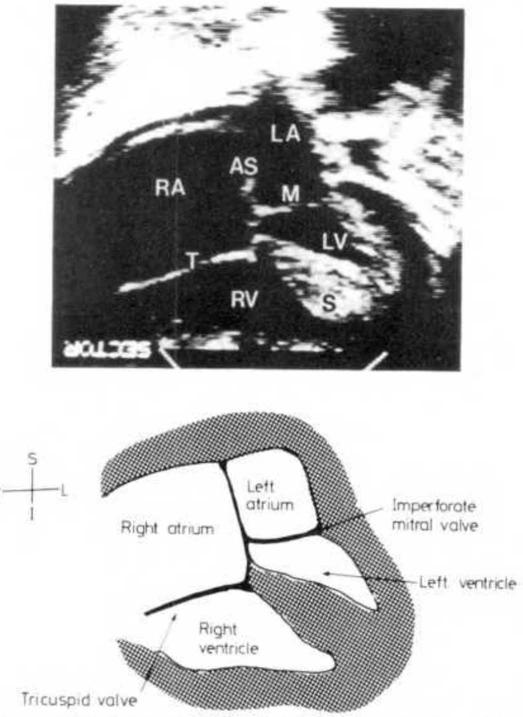

Fig. 4 *Apical view of the same heart shown in Fig. 3a and 3b. This frame is taken during systole and shows that the septal leaflet of the tricuspid valve (T) divides the interventricular septum into atrioventricular and interventricular parts because the tricuspid is attached further towards the apex than the mitral valve. The left atrium (LA) and left ventricle (LV) are relatively hypoplastic. S, interventricular septum; RA, right atrium; RV, right ventricle.*

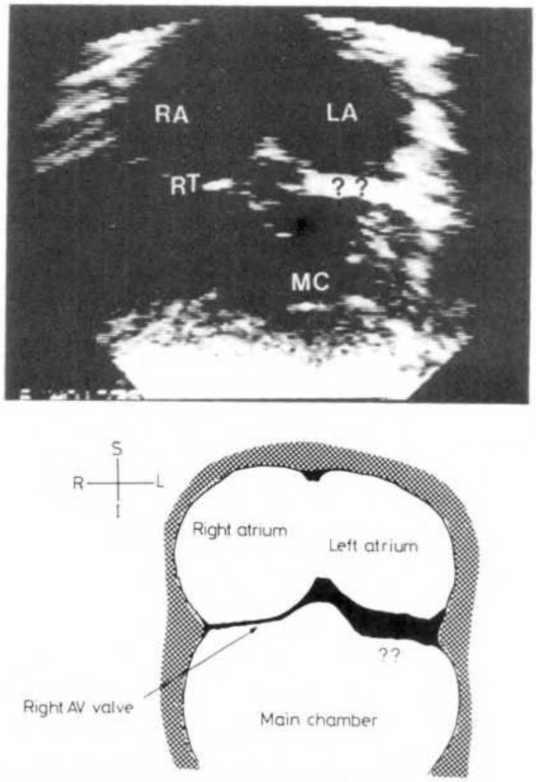

Fig. 5 *Apical view of a univentricular heart in which differentiation of absent left atrioventricular connection from an imperforate left atrioventricular valve was difficult. There appears to be potential communication between the left atrium (LA) and the main chamber (MC) through a thick membrane (??). This could be either sulcus tissue or a thickened imperforate valve. No tensor apparatus is seen and this is considered to be an example of absent left connection. RA, right atrium; RT, right atrioventricular valve.*

unequivocal diagnosis of imperforate valve cannot be made. It seems likely, therefore, that we have occasionally failed to recognise some examples, but nevertheless an accurate demonstration of the mode of atrioventricular connection is possible in the majority of cases.

We are unaware of any other description of the two dimensional echocardiographic appearances of imperforate valves, though recognition by combining angiographic appearances and M-mode echocardiography has been reported.[6] In four of our patients, two with an imperforate right and two with an imperforate left atrioventricular valve, the M-mode echocardiogram disclosed the features of double inlet univentricular heart with two atrioventricular valves, though in each case selective atrial angiography has shown only one perforate valve. It seems therefore that ballooning of an imperforate valve into the ventricle during diastole mimicked the M-mode echocardiographic features of a perforate valve (Fig. 6).

The clinical presentation of absent right or left atrioventricular connection can be mimicked not only by an imperforate valve but also by severe stenosis of the right or left atrioventricular valve, respectively. In some of these cases selective atrial angiography, or for that matter contrast echocardiograms, should distinguish severe stenosis from an imperforate membrane. One of our patients was thought to have atrioventricular concordance with an imperforate tricuspid valve, using both two dimensional echocardiographic and angiographic criteria, and underwent successful tricuspid valvotomy. At operation, however, a very small tricuspid valve orifice was found though the valve appeared to be functionally imperforate. From the clinical standpoint, distinction between a truly imperforate valve and severe stenosis may be impossible.

With the demonstration by Fontan and Baudet that radical palliative surgery is possible for classical

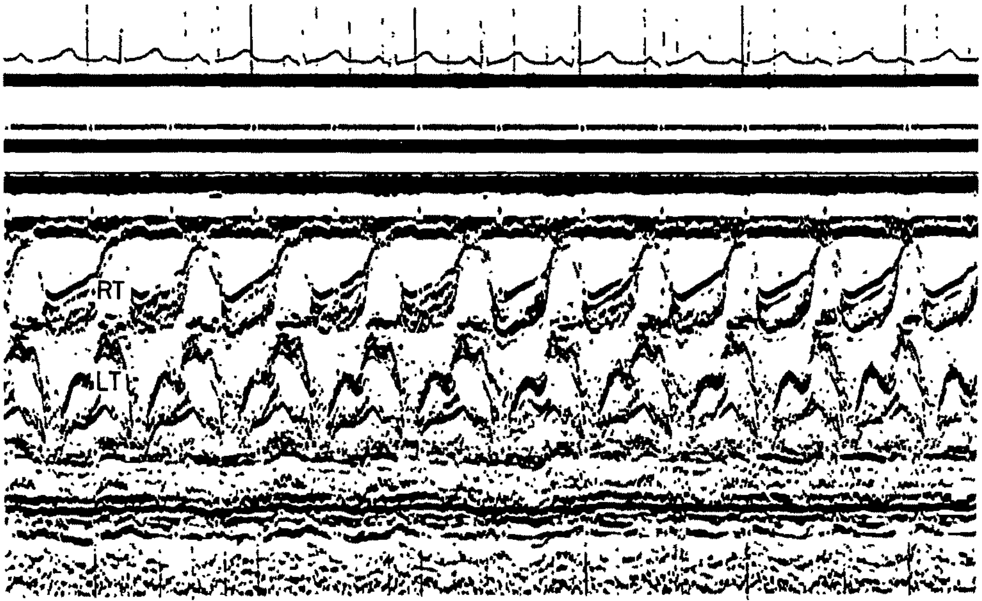

Fig. 6 *M-mode echocardiogram of a double inlet univentricular heart with an imperforate right atrioventricular valve (RT). The appearances are of a double inlet univentricular heart with two perforate valves because there is diastolic apposition of the left atrioventricular valve (LT) and the right atrioventricular valve. The two dimensional echocardiogram showed an imperforate right atrioventricular valve and this was confirmed by selective right atrial angiography.*

tricuspid atresia,[20] accurate description of the anatomy of the atrioventricular junction has become essential. It is evident from our own experience that hearts with atrioventricular concordance and an imperforate tricuspid valve can in some cases be managed by tricuspid valvotomy rather than by a Fontan procedure. If the imperforate valve is hypoplastic, however, or lacks any tensor apparatus the latter may be preferable.

Our study has shown the value of two dimensional echocardiography in the diagnosis of patients in whom the mode of atrioventricular connection is through one perforate and one imperforate valve. We have shown that in these hearts the distinction between atrioventricular concordance and double inlet univentricular heart can be readily made. It must be emphasised that while the majority of patients presenting with tricuspid or mitral atresia will have absence of the right or left atrioventricular connection, respectively, a small number will have an imperforate valve, the identification of which may alter the surgical options available.

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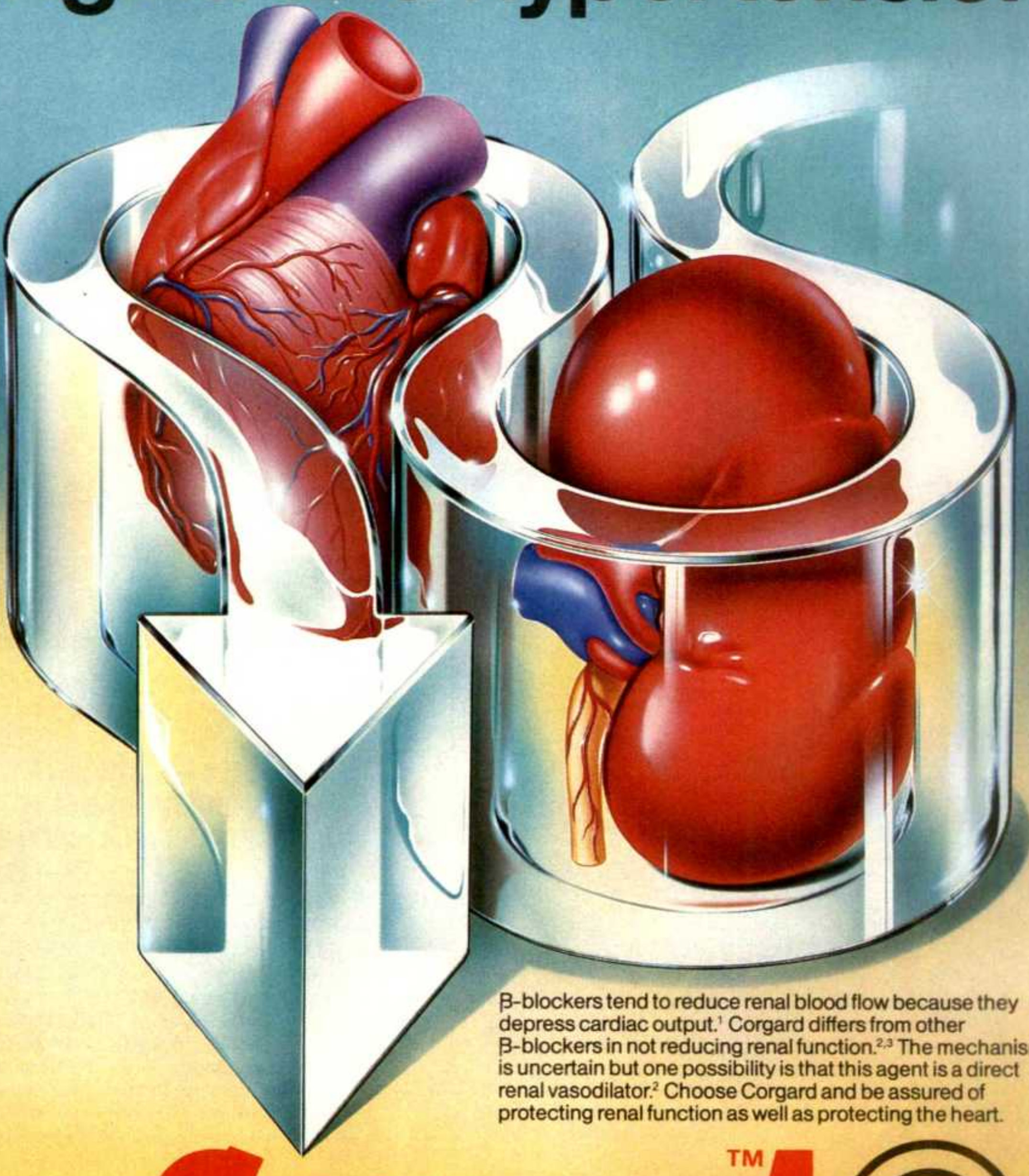

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1. Lancet 1980; 1: 693 2. Br J clin Pharm 1979; 7: (Suppl 2) 219S 3. In: Gross F, ed. International Experience with Nadolol – a long-acting β-blocking agent: symposium, Paris, December 5–7, 1980 London: R Soc Med No 37 1981 25–30

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Br Heart J 1982; 47: 337–43

Abnormal aortic valve echoes in mitral prolapse
Echocardiographic features of floppy aortic valve

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SUMMARY The following distinctive combination of M-mode and two dimensional echocardiographic abnormalities of the aortic valve was observed in a group of 12 patients, of whom 11 had mitral valve prolapse. On two dimensional scans, the aortic cusps were freely mobile but appeared thickened or folded. On M-mode records, cusp excursion was normal: there was well defined systolic oscillation, and cusp echoes were multiple and centrally positioned within the aortic root during diastole.

The aortic valve was inspected at operation in two patients: a typically myxomatous valve was replaced in one and findings were in keeping with this diagnosis in the other. It is suggested that the echocardiographic features described are characteristic of the floppy aortic valve.

Despite the echocardiographic abnormalities, only three patients had clinical evidence of an aortic valve lesion. It is, therefore, further suggested that the investigation of patients with mitral prolapse should include echocardiographic assessment of the aortic valve, even when associated myxomatous degeneration of that valve is not suspected clinically.

This paper describes a distinctive combination of M-mode and two dimensional echocardiographic abnormalities seen in a group of patients with mitral valve prolapse. It is suggested that these echocardiographic abnormalities are characteristic of the floppy aortic valve.

Patients

Twelve patients (Table) were noted to have a distinctive combination of M-mode and two dimensional echocardiographic abnormalities of the aortic valve. The patients (nine men: three women) presented over a five year period: their ages at presentation ranged from 15 to 72 (mean 49) years. There was auscultatory evidence of mitral regurgitation in nine patients, of both mitral and aortic regurgitation in two, and of isolated aortic regurgitation in one. No patient had previous or current infective endocarditis. None was judged to have the clinical features of Marfan's syndrome but two did have congenital scoliosis of the thoracic spine.

Three patients (cases 1, 2, and 3) underwent cardiac catheterisation: all were found to have severe mitral regurgitation. None had an aortic systolic gradient. Angiographic assessment of the aortic valve was omitted in case 1: modest aortic regurgitation was demonstrated in case 2 and there was no evidence of aortic regurgitation in case 3. These three patients proceeded to operation and a typically floppy mitral valve was replaced in each.

Though it had not been suspected clinically, significant aortic regurgitation was found at operation in case 1. The aortic root was dilated and the aortic valve was tricuspid. The cusps were thin and voluminous and the right coronary cusp was fenestrated in several places: the appearances were considered typical of myxomatous degeneration and the valve was replaced. In case 2, the aortic root was of normal size and the valve was tricuspid: rolling of the edges of each commissure was reported but as the cusps appeared to meet adequately in the mid-line, the valve was not replaced. Inspection of the aortic valve was omitted in case 3.

Methods

M-mode echocardiograms were recorded with a

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Table *Patients, auscultatory findings, and results of M-mode echocardiography*

Case No.	*Age/Sex*	*Murmurs*	*M-mode echocardiogram*						*Comments*
			Aortic root (cm)	*Aortic valve*		*Mitral prolapse*	*Left atrium (cm)*	*Fractional shortening %*	
				Systolic oscillation	*Diastolic echoes*				
1	57 M	MR	4·8	++	+++	+	4·8	23	MVR, AVR
2	55 F	MR, AR	2·7	+	+++	+	5·5	29	MVR
3	55 M	MR	3·2	+++	++	+	4·7	23	Scoliosis, MVR
4	69 M	MR	4·9	++	++	+	4·7	23	
5	65 F	AR	3·3	+++	++	−	3·5	41	
6	66 M	MR, AR	3·4	++	++	+	2·0	48	
7	63 M	MR	3·2	++	++	+	4·2	31	
8	17 M	MR	4·2	+++	+++	+	2·1	34	WPW
9	72 M	MR	3·0	+++	++	+	4·8	34	Flail mitral
10	23 M	MR	3·1	++	+++	+	2·0	29	
11	15 M	MR	2·7	++	++	+	2·3	32	
12	34 F	MR	3·3	++	++	+	2·2	43	Scoliosis

MR, mitral regurgitation; AR, aortic regurgitation; MVR, mitral valve replacement; AVR, aortic valve replacement; WPW, Wolff-Parkinson-White syndrome.

2·25 MHz transducer and either a Picker Echoview 80C or a Smith-Kline Eskoline 20 ultrasound system interfaced with a Honeywell strip chart recorder. In making measurements from the M-mode echograms, the criteria recommended by the American Society of Echocardiography[1] were followed. The aortic root and the left atrium were judged to be dilated when their echocardiographic dimensions exceeded 3·7 cm and 4·0 cm, respectively.[2] The lower limit of normal for fractional shortening of the echocardiographic dimension of the left ventricle was taken as 28%.[3]

In case 1, two dimensional echocardiograms were obtained with a linear array (Organon Teknika Echocardiovisor) and only long axis imaging was feasible. In the remaining patients, both the long and short axes were imaged, using either a prototype or a commercially available (Varian V3000) phased array. The images were recorded on viedotape. Figs. 1, 2, and 3 were photographed from the videotape replay and Fig. 4 was photographed, at the time of examination, from the primary oscilloscope display. In all the illustrations, timing is indicated by the right hand edge of the electrocardiogram.

Results

AORTIC ROOT AND AORTIC VALVE

(a) M-mode echocardiography (Table and Fig. 5, 6, 7, 8)
Four patients had a dilated aortic root. Aortic cusp echoes appeared slightly thickened: they separated widely in systole and in six patients, three cusps were defined (Fig. 8). Pronounced systolic oscillation (Fig. 5, 6, 7) was a constant feature: it was very gross in some instances (Fig. 8). In diastole, cusp echoes were multiple and centrally positioned within the aortic root (Fig. 5, 6, 8). There was no evidence of prolapse of cusp tissue into the left ventricular outflow tract.

(b) Two dimensional echocardiography (Fig. 1, 2, 3, 4)
Bright echoes were recorded from the aortic cusps and these appeared thickened or folded. On long axis views, cusp mobility was seen to be unrestricted and systolic oscillation of the free edge of the leaflets was observed. Prolapse of cusp tissue into the left ventricular outflow tract was suspected in two patients. Short axis imaging defined three aortic cusps (Fig. 3) in the 11 patients examined. Apparent thickening or folding of the leaflets was most obvious when the valve was closed (Fig. 3a, 4c): systolic separation was wide and the valve orifice was unobstructed (Fig. 1b, 3b, 4b).

MITRAL VALVE (Table)

Eleven patients had classical M-mode evidence of mitral valve prolapse; diastolic excursion of the mitral anterior leaflet was increased and systolic sagging of the leaflets extended from 3 to 10 mm behind the C point of the mitral echogram. A partially flail posterior leaflet was suspected in case 9 (Fig. 7). Long axis two dimensional imaging in these patients was consistent with mitral prolapse.

The remaining patient (case 5) also had a nonrheumatic mitral valve (Fig. 4): mild mitral prolapse was thought to be possible but unequivocal diagnostic features were lacking.

LEFT ATRIUM (Table)

The left atrium was dilated in six patients, including the three who were operated on.

LEFT VENTRICLE (Table)

Fractional shortening of the echocardiographic dimension of the left ventricle was reduced in three patients, including two of those operated on.

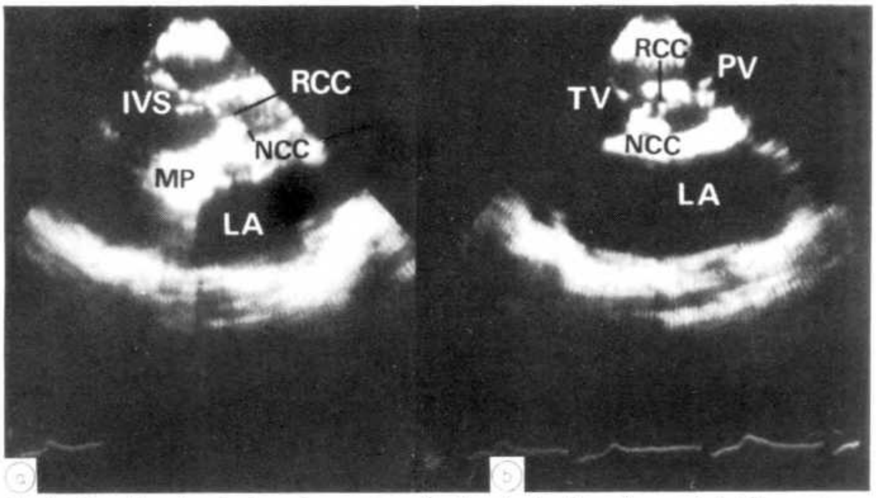

Fig. 1 *Two dimensional echocardiograms (case 2, after mitral valve replacement): (a) Long axis, diastole. (b) Short axis, early systole. The right (RCC) and non-coronary (NCC) cusps have been identified in both views. The non-coronary cusp appears thickened or folded: the aortic valve orifice is unobstructed. On the real-time display, vigorous systolic oscillation of the right coronary cusp was seen in the long axis view. IVS, interventricular septum; MP, mitral prosthesis; LA, left atrium; TV, tricuspid valve; PV, pulmonary valve.*

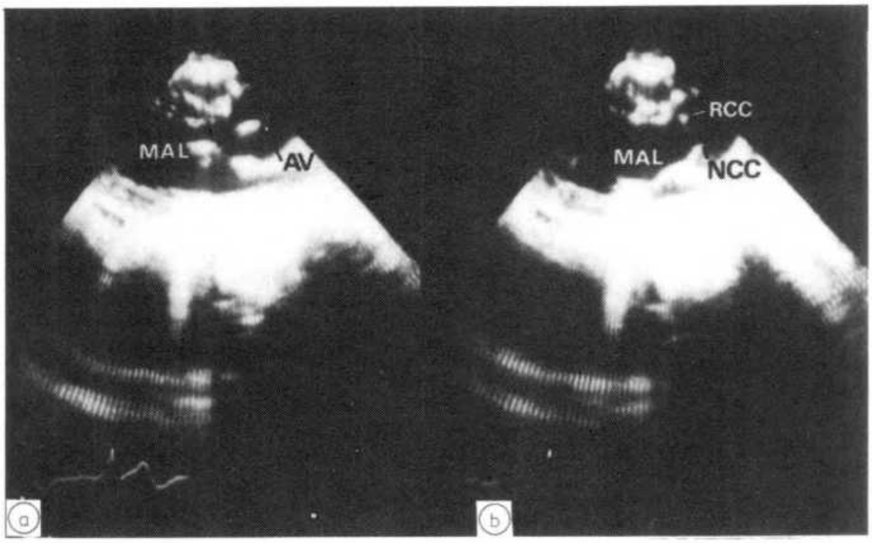

Fig. 2 *Long axis two dimensional echocardiograms (case 8) in (a) diastole and (b) early systole. The aortic cusps appear thickened: diastolic apposition is normal. Systolic oscillation of both cusps was seen on the real-time display. The mitral anterior leaflet appears thickened and elongated. AV, aortic valve, MAL, mitral anterior leaflet.*

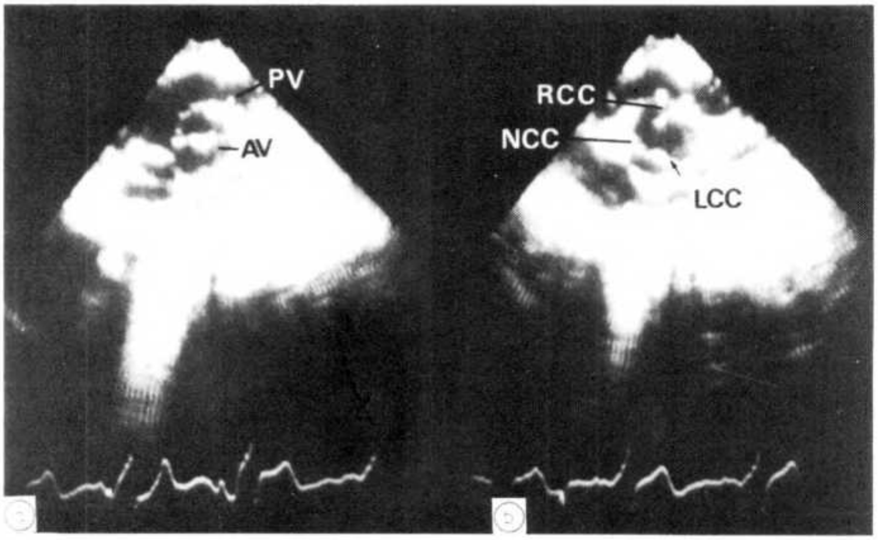

Fig. 3 *Short axis two dimensional echocardiograms (case 8) at (a) end-diastole and (b) late systole. The closed aortic valve appears thick. In the open position, three cusps are seen: all look thickened or folded but an adequate aortic orifice is maintained. LCC, left coronary cusp.*

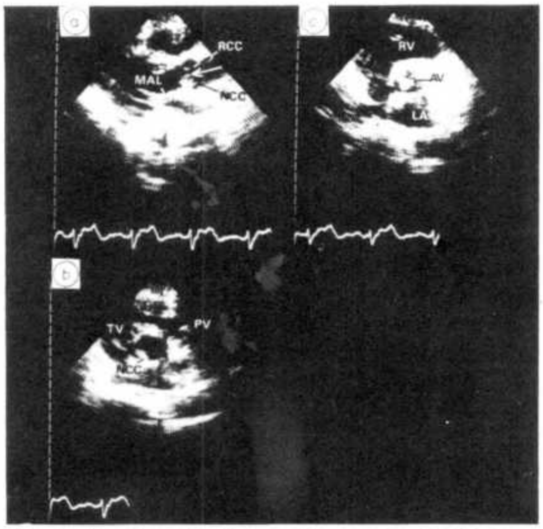

Fig. 4 *Two dimensional echocardiograms (case 5). (a) Long axis, systole. (b) Short axis, late systole. (c) Short axis, early systole. The closed aortic valve appears thickened (c). In the open position, thickening or folding appears particularly to involve the non-coronary cusp: the aortic orifice is unobstructed. The structure arrowed in (a) is probably the left coronary cusp.*

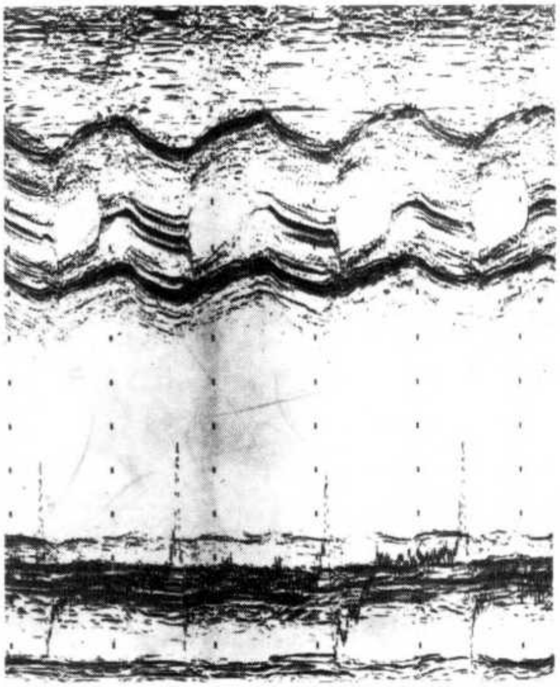

Fig. 5 *M-mode echocardiogram of aortic valve (case 2, after mitral valve replacement). Systolic excursion of the cusps is normal: there is fine systolic oscillation. Cusp echoes are multiple and centrally positioned throughout diastole.*

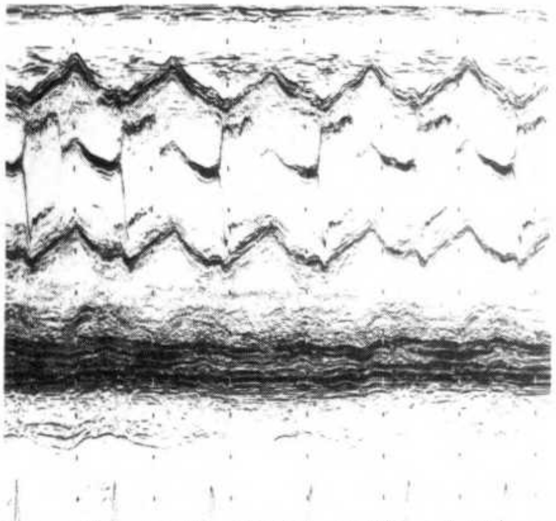

Fig. 6 *M-mode echocardiogram (case 8). The aortic root is dilated. Systolic excursion of the cusps is normal. There is well-defined systolic oscillation of both cusps. Cusp echoes are multiple in mid and late diastole and centrally positioned throughout diastole.*

Discussion

Our patients were selected on the basis of a distinctive combination of echocardiographic abnormalities of the aortic valve. All but one of them was found also to have classical echocardiographic evidence[4 5] of mitral valve prolapse and a typically floppy mitral valve was shown in the three who were operated on. One of our patients (case 1) undoubtedly had a floppy aortic valve and operative findings were in keeping with this diagnosis in another (case 2). As it is established that myxomatous degeneration of the mitral valve may, on occasion, be associated with myxomatous degeneration of the aortic valve,[6-9] it is not unreasonable to speculate that the remaining patients also had floppy aortic valves.

On the two dimensional scans, the aortic cusps looked thick and, on static images, could easily have been thought to be calcified. Viewed in movie format, however, they were clearly freely mobile and there was oscillation of their free edges. M-mode records confirmed the mobility and the systolic oscillation and showed that, at most, there was only minimal thickening of the free edges of the leaflets. Thus, despite the two dimensional appearances, the cusps were obviously not in fact thick, and we suggest that folding of

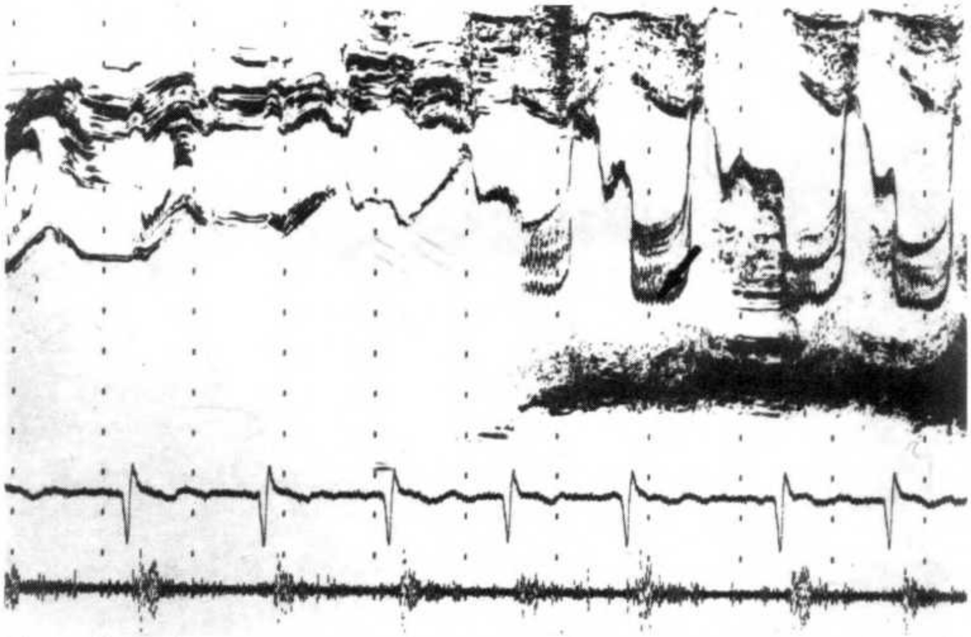

Fig. 7 *Phonocardiogram and M-mode sweep from aorta to mitral valve (case 9). Systolic excursion of the aortic cusps is normal: there is systolic oscillation of the non-coronary cusp and apparent thickening of the right coronary cusp. In diastole, aortic cusp echoes are multiple and anteriorly displaced. Diastolic excursion of the mitral anterior leaflet is increased. There is pansystolic sagging of the mitral echogram: systolic vibration (arrowed) suggests that the valve is partially flail.*

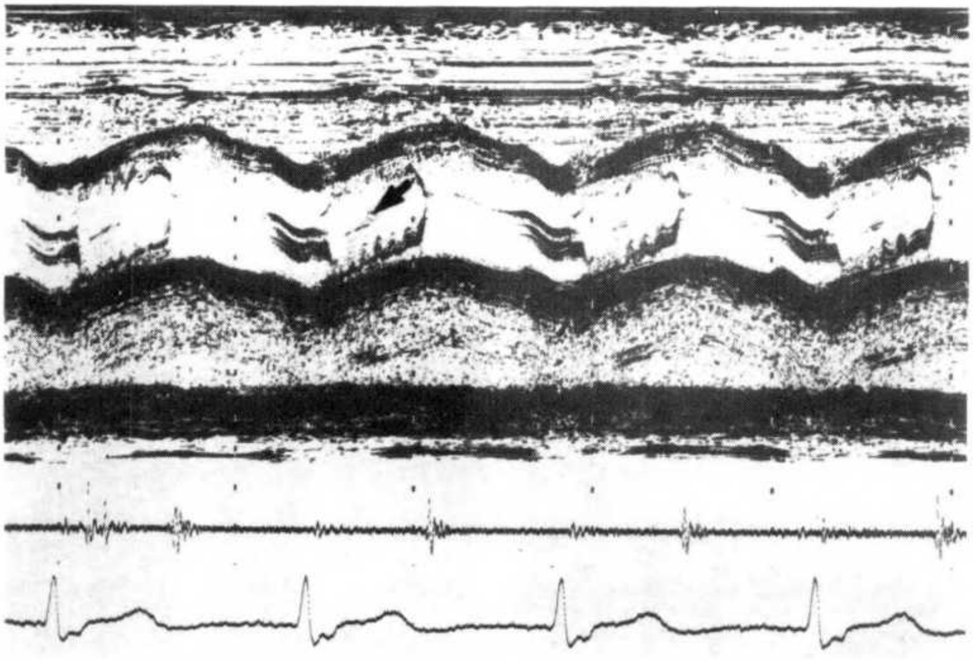

Fig. 8 *M-mode echocardiogram and phonocardiogram from the patient with an isolated aortic diastolic murmur (case 5). Echoes have been recorded from all three aortic cusps (the left coronary cusp is arrowed). Cusp excursion is normal: there is coarse systolic oscillation. Cusp echoes are multiple in mid and late diastole and centrally positioned throughout diastole.*

redundant cusp tissue could account for the apparent thickening of the two dimensional images and for the multiple diastolic echoes on the M-mode records.

We have proof of a floppy aortic valve in a patient with mobile but apparently thickened aortic cusps on two dimensional images and with systolic oscillation of the cusps and multiple diastolic cusp echoes on the aortic M-mode echogram. We suggest that this combination of M-mode and two dimensional echocardiographic abnormalities, which has not been described previously, is characteristic of the floppy aortic valve.

It must be stressed that it is the combination of echocardiographic abnormalities which we regard as characteristic of the floppy aortic valve: considered in isolation, some of the features could be otherwise explained. Thus, systolic oscillation of the aortic valve (without apparent thickening) is a non-specific finding, and both calcified[10] and bicuspid[11] aortic valves have echocardiographic features similar to some but not to all of those recorded in our patients.

There have been no previous decriptions of the two dimensional echocardiogram recorded from a floppy aortic valve and little has been written about the M-mode findings. Chandraratna *et al.*'s account[12] of diastolic fluttering and diastolic separation of the cusp echoes in a patient with a non-infected, regurgitant, myxomatous aortic valve is at variance with the present M-mode findings. This report, however, also noted systolic oscillation and Chandraratna suggested that multiple diastolic echoes might be recorded from a single redundant cusp, giving the appearance of cusp separation. Rippe et *al.*[13] recorded M-mode echograms in four patients with regurgitant myxomatous aortic valves. Three of their patients had dilatation of the aorta and the valve looked normal though its excursion was small in relation to the aortic root. More in keeping with the present observations, they mentioned (but did not describe) additional abnormal aortic echoes which were present in two patients and were thought possibly to reflect leaflet redundancy. In another patient, high frequency systolic vibration of the aortic cusps was noted without comment.

Aortic regurgitation is a recognised feature of Marfan's syndrome. It is often attributed solely to dilatation of the aortic root but there is evidence that myxomatous degeneration of the aortic valve may be an additional causal factor.[14] With this in mind, it is interesting to note the M-mode features which we have ascribed to the floppy aortic valve, in the published echograms of patients who had Marfan's syndrome with dilatation of the aortic root and mitral prolapse.[15 16]

Thus, careful scrutiny of previous reports provides evidence to support our contention that the M-mode features which we have described are characteristic of the floppy aortic valve. In our M-mode examinations we took care always to record maximal separation of the aortic cusps and to note any changes which occurred with slight alterations in the direction of the ultrasound beam. It is possible that previous workers did not do so and this may explain why they did not consistently observe the M-mode features described here.

An aortic valve lesion was suspected clinically in only three of our patients. As there are no known characteristic auscultatory features, floppy aortic valves are likely to be recognised clinically only when they become infected or when they become spontaneously regurgitant. Thus, though there have been studies of surgical and necropsy material,[9 17] the true incidence of myxomatous degeneration of the aortic valve is at present unknown. It appears from the present study that echocardiographic surveys might provide the information.

Further validation is necessary, but we suggest that the combination of M-mode and two dimensional echocardiographic abnormalities which we have described can be regarded as diagnostic of a floppy aortic valve. We recommend that the investigation of patients with mitral prolapse should include echocardiographic assessment of the aortic valve even when associated myxomatous degeneration of that valve is not suspected clinically.

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Straddling atrioventricular valve with absent atrioventricular connection
Report of 10 cases

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SUMMARY Six hearts with absent right connection and four hearts with absent left connection in association with straddling of an atrioventricular valve are described. Their categorisation is made easier by adopting a segmental approach. The conduction tissue was studied in two hearts and the arrangements were unusual.

Straddling of an atrioventricular valve may be defined as the arrangement in which its tension apparatus is attached to both sides of the ventricular septum.[1 2] When defined as such, the most frequent example of a straddling valve is an atrioventricular septal defect with a common atrioventricular orifice ("complete endocardial cushion defect" or "complete atrioventricular canal malformation"), though some authorities question whether "straddling" should be used in this context.[3 4] Less frequent are the hearts in which there are two atrioventricular valves and either the right valve or the left valve, or, exceptionally, both valves, have their tension apparatus attached to both sides of the septum.[2-4] These hearts pose a major problem in surgical treatment.[1] Hearts have also been reported, however, in which either the right or left valve straddles when the other valve is atretic. These latter hearts are exceedingly rare,[3 5-8] but they pose particular problems in classification, particularly concerning their relation to common atrioventricular orifice.[9] We have now examined 10 such hearts from various centres and studied their morphology and, in two cases, the distribution of their conduction tissues. The unusual findings encountered form the basis of this report.

Definitions and terms

A *straddling atrioventricular valve* is one in which the tension apparatus is attached to both sides of a ventricular septum. Usually when an atrioventricular valve straddles, its annulus is committed to both chambers in the ventricular mass. The degree of commitment is termed the *override*, and is described according to the percentage of the valve annulus attached to each ventricular chamber.

It is our convention in hearts with overriding valves to distinguish the atrioventricular connection present according to the precise connection of the abnormal valve. Thus, the atrioventricular connection must be either double inlet, or else concordant, discordant, or ambiguous according to the morphology of the chambers connected together. Irrespective of the connection, of necessity one of the ventricular chambers must be more or less rudimentary while the other ventricle will unequivocally be the main or primary chamber. When one atrioventricular orifice is atretic and the other orifice overrides, this condition does not apply. There is always absence of one atrioventricular connection. The sole remaining ventricular inlet por-

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†RHA is also Honorary Senior Lecturer to The Hospital for Sick Children and Honorary Lecturer to the University of Liverpool.

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tion, together with the straddling valve, is then shared between the two ventricular trabecular components, meaning that both ventricular chambers are more or less rudimentary. None the less, except when the override is exactly equal, one of the chambers can be nominated as the main ventricular chamber and the other as the secondary chamber. It is also possible to describe the pattern of ventricular architecture present. For the sake of clarity, the overriding valve will be described simply as right or left, depending on whether it drains the right-sided or left-sided atrium.[8] But, for those who wish to know whether the valve is basically tricuspid (morphologically right) or mitral (morphologically left), this can be deduced knowing the atrial situs and ventricular architecture of a given heart. Where the valve was recognisably mitral or tricuspid, this was stated.

Material and methods

Ten hearts were included in the study (Table). They came from cardiological collections of the Brompton Hospital, London; The Hospital for Sick Children, London; Royal Liverpool Children's Hospital; Killingbeck Hospital, Leeds; Grimsby General Hospital; Newcastle General Hospital, Newcastle; Wilhelmina Gasthuis, Amsterdam; and the State University Hospital of Leiden.

Careful studies of each heart were undertaken to determine the segmental arrangement and the degree of override of the straddling valve. This was done by viewing the annulus of the valve from its atrial side and thus determining the degree of commitment of the annulus to each of the ventricular chambers. Two hearts were studied so as to determine the disposition of their conduction system, using the technique described by Smith *et al.*[10] The cardiac apex and top of the atria were removed, leaving the atrioventricular junction. The heart with left atrioventricular valve atresia was then divided into three blocks—a left parietal, a right parietal, and a septal block. The heart with right atrioventricular valve atresia was processed as one piece after the removal of the left parietal wall. Serial sections were cut from each block at 10 μm thickness. All the sections were kept and every 25th section mounted and stained with the Masson's trichome technique. Further sections were mounted and stained wherever deemed necessary.

Results

The hearts studied could be divided into two basic groups, those with absent right atrioventricular connection (atresia of the right atrioventricular valve) and those with absent left connection (atresia of the left atrioventricular valve). The hearts were further subdivided into two groups according to the trabecular morphology of the main ventricular chamber, that is of right or left ventricular type. The position and the morphology of the atrioventricular valves were also noted. In each of these groups, we identified hearts with rudimentary secondary ventricular chambers to the left or to the right of the main chamber, the morphological pattern always being complementary to that of the main chamber. Among the hearts studied, six had absent right and four had absent left atrioventricular connection.

HEARTS WITH ABSENT RIGHT ATRIOVENTRICULAR CONNECTION

In this group, four hearts had a main chamber with right ventricular trabecular pattern and two had main chambers of left ventricular type. The rudimentary chamber of left ventricular morphology was positioned to the right and posterior to the main chamber in cases 1-3 (left-hand pattern ventricular architecture—Fig. 1) and to the left and posterior in case 4 (right-hand pattern ventricular architecture). In the two specimens with rudimentary secondary chamber of right ventricular type, the rudimentary chamber was right anterior in one case (right-hand pattern) and left anterior in the other (left-hand pattern). In this respect the terms "right-hand pattern" and "left-hand pattern" are used to describe the ventricular architecture as suggested by Van Praagh and his colleagues[11] and are independent of either the atrioventricular connection or the ventricular relation.

The straddling and overriding valve in this group was the left atrioventricular valve. Its morphology was as anticipated from the presumed ventricular architecture in all cases. In the three cases with left-hand pattern architecture, the left-sided atrioventricular valve was a morphologically tricuspid valve. In the case with right-hand architecture in which the main chamber was of right ventricular morphology the atrioventricular valve was bicuspid in appearance. Both the left valves in the hearts with left ventricular main chambers were of mitral morphology. The least commitment of the atrioventricular valve to the main chamber in this group was 65% and the maximum was 80%. The trabecular septum in the hearts with main chambers of right ventricular type was without exception found to extend to the crux cordis. In the hearts with main chambers of left ventricular type, the septum extended to the crux in one but was an anterior structure in the other heart.

The ventriculoarterial connections varied. Three of the four hearts with right ventricular main chambers had double outlet from the main chamber and the other had pulmonary atresia, the aorta arising from the main chamber. The two specimens with main chamber of left ventricular morphology had discor-

Table *Hearts studied*

Mode of connection chamber	*Main chamber morphology*	*Position and morphology of rudimentary chamber*	*Straddling valve*	*Septum to crux*
Absent right connection	Right ventricular type	Left ventricular type right posterior	LAVV(TV)	Yes
			LAVV(TV)	Yes
			LAVV(TV)	Yes
		Left ventricular type left posterior	LAVV(MV)	Yes
	Left ventricular type	Right ventricular type right anterior	LAVV(MV)	Yes
		Right ventricular type left anterior	LAVV(MV)	No
Absent left connection	Right ventricular type	Left ventricular type left posterior	RAVV(TV)	No
			RAVV(TV)	Yes
	Left ventricular type	Right ventricular type right anterior	RAVV(TV)	No
		Right ventricular type left anterior	RAVV (indeterminate)	No

LAVV, left atrioventricular valve;
RAVV, right atrioventricular valve;
MV, morphologically mitral valve;
TV, morphologically tricuspid valve;
DOMC, double outlet main chamber;
DORC, double outlet rudimentary chamber;
PA, pulmonary atresia;
ASD, atrial septal defect;
PFO, patent foramen ovale;
PDA, persistent ductus arteriosus;
LSVC, left superior vena cava

dant ventriculoarterial connections. The aorta was anterior to the pulmonary trunk or its atretic remnant in two cases, right anterior in three cases, and left anterior in the other. A common finding in all specimens of this group was an interatrial communication, either a patent foramen ovale or a secundum atrial septal defect. Interruption of the aortic arch was found in case 1.

HEARTS WITH ABSENT LEFT ATRIOVENTRICULAR CONNECTION

Four hearts were found in this group, two (cases 7, 8)

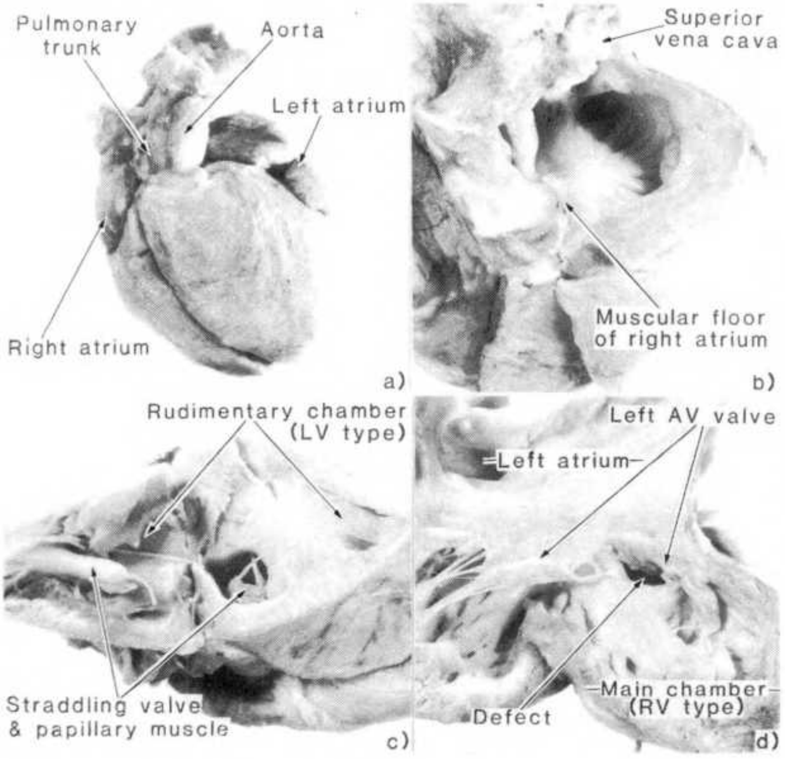

Fig. 1 *The heart from case 1. (a) The heart viewed from the front. The aorta arises anterior and to the left of the pulmonary trunk. (b) The blind-ending right atrium opened and viewed from above and behind. (c) The right-sided rudimentary chamber with left ventricular pattern. The left atrioventricular valve straddles through the septal defect. (d) The left-sided main chamber with right ventricular trabeculations.*

% to main chamber	*Ventriculoarterial connection*	*Aortic position*	*Cardiac position*	*Associated anomalies*	*Case No.*
70%	DOMC	Left anterior	Left	ASD, interrupted arch	1
80%	DOMC	Anterior	Mid-line	PFO	2
80%	PA, aorta from main chamber	Anterior to atretic pulm trunk	Right	PFO, PDA	3
75%	DOMC	Right anterior	Left	Secundum ASD	4
80%	Discordant	Right anterior	Left	PFO	5
65%	Discordant	Right anterior	Not known	PFO	6
70%	DOMC	Right anterior	Left	PFO, persistent LSVC	7
95%	PA, aorta from main chamber	Anterior to atretic pulm trunk	Left	PFO, PDA	8
65%	Concordant	Right posterior	Left	Secundum ASD	9
75%	DORC	Right	Left	PFO	10

with a main chamber of right ventricular morphology (Fig. 2) and two with main chambers of left ventricular morphology (Fig. 3). In hearts with right ventricular main chambers, the rudimentary chamber was found to the left and posterior to the main chamber (right-hand pattern ventricular architecture). The sole atrioventricular valve was a morphologically tricuspid valve, being committed by 70% and 95% to the main chamber. Though the main chamber in both was of right ventricular morphology, the septum extended to the crux cordis only in one. This particular heart was unusual in that though it was in the left chest with its apex directed to the left, the ventricular mass was rotated so that the crux was in relatively anterior position. None the less, the septum between the ventricular chambers still extended to the point where the atrial septum joined the atrioventricular junction. The ventriculoarterial connection was double outlet main chamber, with the aorta right and anterior to the pulmonary trunk in one heart while in the other the aorta arose from the main chamber anterior to the atretic pulmonary trunk.

The two hearts with main chambers of left ventricular morphology had anterior right ventricular rudimentary chambers located to the right in one (right-hand pattern architecture) and to the left in the other (left-hand pattern). Though it drained predominantly (65%) to a main chamber of left ventricular type situated on the left, the atrioventricular valve had a tricuspid morphology in one of these hearts. In the other the atrioventricular valve had four cusps and was neither tricuspid nor mitral in appearance. It was committed by 75% to the main chamber. The septum did not reach the crux in either heart. The ventriculoarterial connection was concordant in one heart, the aorta arising to the right and posterior of the pulmonary trunk. Both great arteries originated from the rudimentary chamber in the other with the aorta to the right of the pulmonary trunk.

CONDUCTION TISSUE DISPOSITION

(a) *With absent right connection, straddling left valve, main chamber with right ventricular morphology, and rudimentary left ventricular chamber in right posterior position (left-hand pattern ventricular architecture)*

The atrioventricular conduction system was in the form of a sling between two atrioventricular nodes (Fig. 4, 5). The posterior node was located in the posterior interatrial septum above the fibrous annulus of the left valve. The penetrating bundle perforated the fibrous annulus and the long non-branching bundle then descended steeply along the posterior septum. The bundle then ran along the crest of the defect beneath some chordae tethering the straddling valve. Towards the anterior rim, the bundle dropped off the edge to the left side and gave off a large right bundle-branch to the left sided morphologically right ventricle. The anterior limb of the bundle ascended sharply as it looped backwards to contact an anterior node. This node was well formed and situated in the right atrial aspect of the anterior part of the atrial septum.

(b) *With absent left connection, straddling right valve, main chamber with left ventricular morphology, and rudimentary left ventricular chamber in left posterior position (right-hand pattern ventricular architecture)*

There was gross malalignment between the atrial septum and the ventricular septum. The atrial septum lined up with the left lateral wall of the heart such that the left posterior quadrant of the right atrioventricular valve straddled the ventricular septum (Fig. 6). Atrioventricular ring conduction tissue was found in clusters at various points around the right atrioventricular orifice on the atrial aspect. The rudimentary left ventricular chamber was very small and a left bundle-branch could be seen on the left side of the septum. This led to a non-branching bundle which ran up a free-running trabecula in the back of the rudimentary chamber. The trabecula was adherent to the septum at its base. The bundle perforated the valve annulus in its posterior border and made contact with an atrioventricular node formed from a cluster of ring tissue in the back of the right atrium. Further to the left but more anteriorly along the orifice there was a cluster of specialised tissue which resembled an atrioventricular node. This node had an arterial supply but did not give rise to a penetrating atrioventricular bundle.

Discussion

Hearts with straddling of one atrioventricular valve and atresia of the other are exceedingly rare. Though difficult to categorise, we have shown that adoption of a segmental approach makes their description much easier. The necessary information for full description is whether the atrium lacking an atrioventricular connection is right- or left-sided. As a corollary the straddling valve must be on the other side. The ventricular architecture together with the relation of the ventricular chambers must then be described and the commitment of the straddling valve to the ventricular chambers must be specified. The ventriculoarterial connection and relations, together with a catalogue of associated malformations, complete the description.

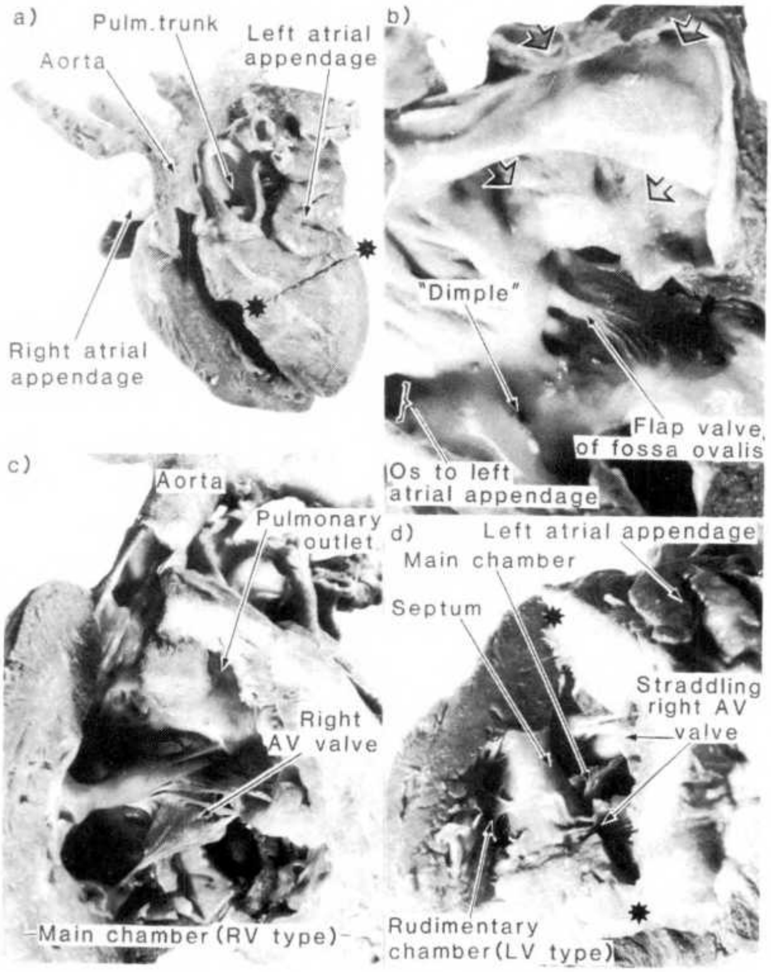

Fig. 2 *(a) The heart from case 7 viewed from the front. The aorta is anterior and to the right of the pulmonary trunk. The asterisks mark the line of dissection shown in (d). (b) A view of the left atrium from the back. The open arrows indicate the orifices of the pulmonary veins. The "dimple" represents the floor of the left atrium but this has no connection with the ventricular mass. (c) The main chamber which receives the main part of the single atrioventricular valve. There is a bilateral infundibulum supporting the outlets. (d) An apical view of the heart displayed by opening the ventricular mass along the line of dissection (asterisks marked in (a)). The right atrioventricular valve straddles into the rudimentary chamber of left ventricular type.*

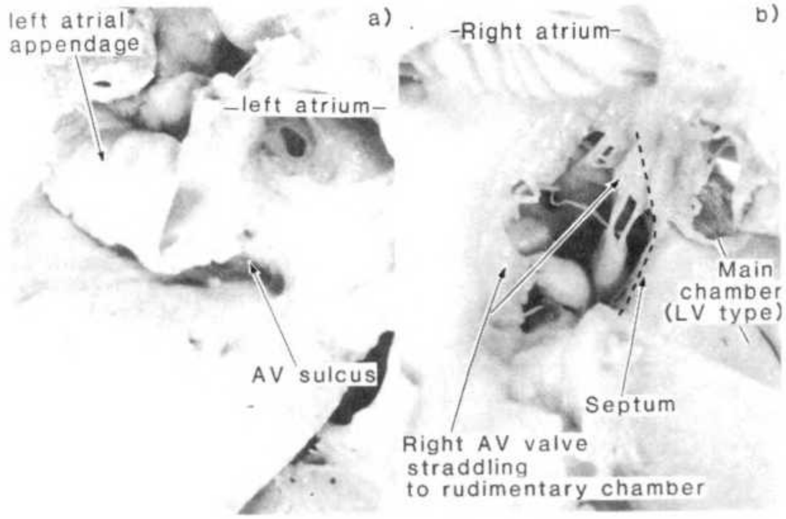

Fig. 3 *The heart of case 10 is viewed from the left in (a). The left atrium has a characteristic hooked left atrial appendage. Atrioventricular sulcus tissue separates the blind-ending left atrium from the ventricular mass. (b) The same heart viewed from the right atrium. The broken line marks the extent of the trabecular septum. Two papillary muscles tether the right atrioventricular valve to the rudimentary chamber which is left anterior in position.*

This can then be augmented by describing the morphology of the straddling valve and determining whether the septum runs to the crux of the heart.

Although use of such an approach gives no difficulties in description, problems are encountered when the hearts are categorised in the hierarchy of congenital anomalies, specifically as to whether they should be considered as having biventricular or univentricular connections. Associated with this are problems in interpretation of the nature of the sole atrioventricular valve, specifically as to whether it is a mitral valve, a tricuspid valve, or a common valve. We now use the terms "biventricular" and "univentricular" simply as a means of grouping together hearts with comparable atrioventricular connections. In hearts with concordant, discordant, or ambiguous connections, each atrium is connected to its own ventricle. These are the hearts we term biventricular. In most hearts with double inlet or with absence of one atrioventricular connection, only one ventricular chamber has an atrioventricular connection and these are the hearts grouped together as having univentricular connections. In hearts with overriding of one of two or a common valve, the connection is determined according to the commitment of the overriding valve and the hearts categorised accordingly as having biventricular or univentricular connections. In the hearts presently described there is clearly a problem. One atrioventricular connection is absent, but both ventricular chambers are connected to the remaining atrial chamber.

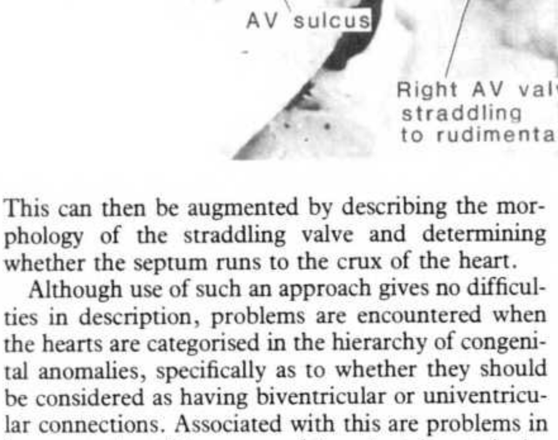

Fig. 4 *Diagram illustrating the distribution of the conduction tissues (hatched area) in case 1. The anterior node is situated in the floor of the right atrium and it connects with a conduction tissue "sling" which also makes contact with a posterior node. The pairs of arrows marked A, B, C, D indicate the planes of sections shown on Fig. 5. Though the right atrium partly overlies the rudimentary chamber, there is no connection between the right atrium and the ventricular mass.*

Since there is only one ventricular inlet portion shared between the ventricular trabecular components, each ventricular chamber is more or less rudimentary. Arguments about whether one chamber is a ventricle and the other not in this context are non-productive, as indeed they have proved to be in all hearts with two ventricular chambers. Both are ventricular chambers. Each is recognisable according to its trabecular pattern as right or left ventricular in type. In each heart we have examined it was possible to determine the pattern of ventricular architecture present,[11] and which ventricular chamber was connected to most of the overriding valve. In the necropsy material studied here we had no problem in making this distinction, the most nearly equal sharing being 65% to one chamber and 35% to the other.

Thus, we had no difficulty in distinguishing a main ventricular chamber from a secondary ventricular chamber. All of this information is required for full description of these complex cases, together with the precise relations of the ventricular chambers. When given in this fashion, the description provided transcends possible arguments as to whether the hearts have univentricular or biventricular connections, or as to whether they are "single" ventricles. With regard to the connection, it does not really matter. With regard to "singleness", they clearly have two ventricular chambers. Some have categorised the hearts as "double outlet atrium."[7-9] This is certainly an accurate description, but it should be recognised that it is equally applicable to all hearts with straddling of a right or left valve. If used, therefore, it must be qualified by description of absence of the other atrioventricular connection.

Concerning the morphology of the sole valve present, in most of the hearts studied it was as expected for the ventricular architecture present. Thus, in hearts with right ventricular main chambers, the left-handed valve was a tricuspid valve with left-hand pattern ventricular architecture and a mitral valve with left-hand pattern architecture. The association was less perfect when the main chamber was of left ventricular morphology. But this is to be expected, since, when there is double inlet to a left ventricular chamber, both the valves resemble mitral valves.[12] Some have suggested that the sole valve is a common valve.[8,9] Though on occasions the valve had morphological features of a common valve, in all cases it drained only one atrial chamber. We believe the term "common valve" should be reserved for those valves draining both atrial chambers. The valves in these hearts are best described as simply right valves or left valves depending on whether they drain the right-sided or left-sided atrial chambers, respectively. This convention is unambiguous and cannot lead to confusion. Morphology of the valve can always be specified if required, and can usually be inferred from the ventricular architecture present. It should also be appreciated that the nature of the atretic valve can also be inferred from the ventricular architecture for those

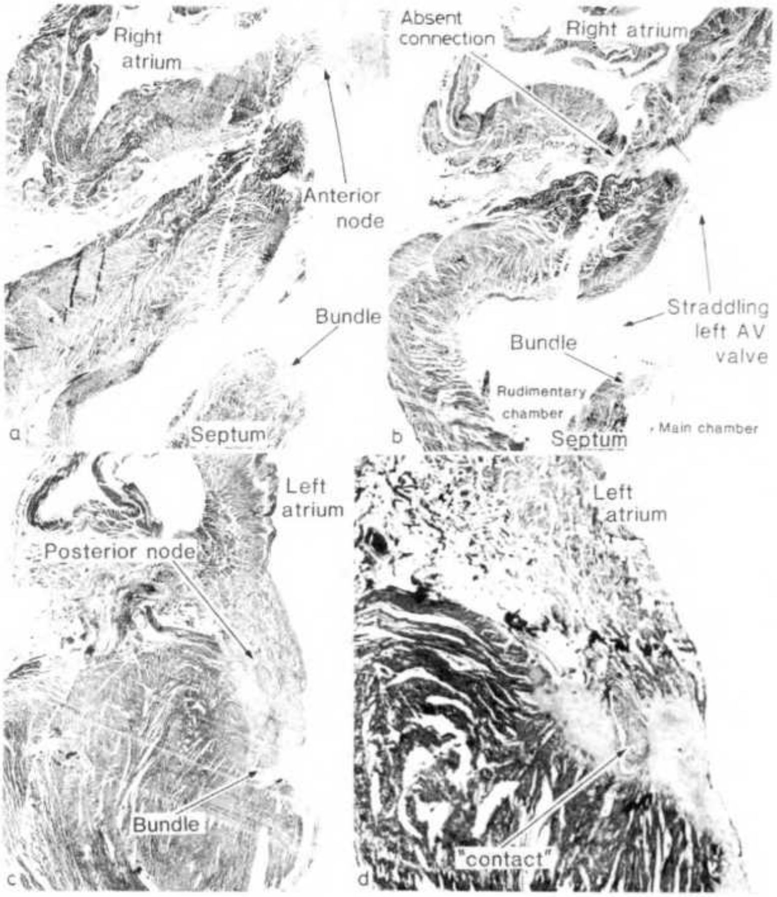

Fig. 5 *Histological sections from case 1 taken through the planes shown on Fig. 4. (a) The anterior node situated in the anteromedial margin of the right atrium. The anterior limb of the bundle is seen on the crest of the septum. (b) The sulcus tissue between the floor of the right atrium and the rudimentary chamber. The left atrioventricular valve straddles the tabecular septum. The posterior limb of the bundle is seen in (c) and it penetrates the fibrous annulus to make contact with a posterior node (d) which is on the left atrial aspect.*

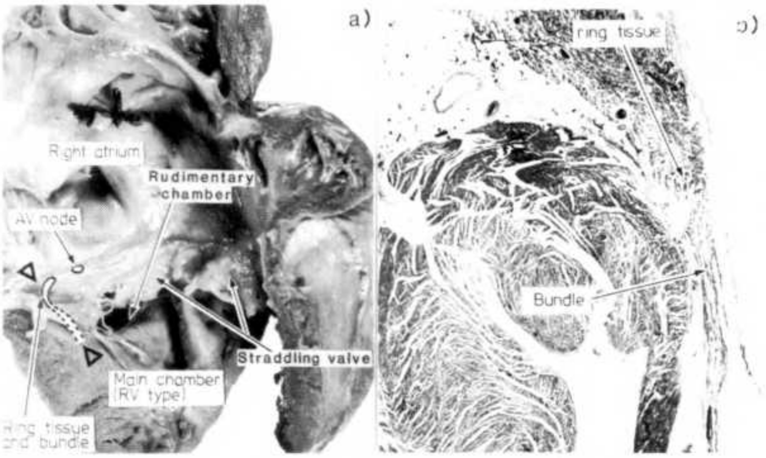

Fig. 6 *(a) The heart from case 7 displayed to show the right atrium opening into the main chamber. The right atrium opens partly to the left posterior rudimentary chamber and mainly into the main ventricular chamber because of the malalignment between the atrial septum and trabecular septum. The open arrows indicate the plane of section shown in (b).*

who are concerned with morphogenesis. Thus, in our grouping of hearts in terms of absent right or absent left connection, we have included cases together which can be interpreted in terms of mitral or tricuspid atresia. For those requiring knowledge of the presumed morphology of the atretic valve, this can be inferred knowing the situs, the ventricular architecture, and which connection is absent.

The conduction tissue was unusual in both the hearts we examined morphologically. Both hearts had the straddling valve, of tricuspid morphology, committed in its greater part to a right ventricular chamber. In one of the hearts, it was the left connection which was absent and the rudimentary left ventricular chamber was left-sided (right-hand pattern architecture). The trabecular septum did not reach the crux and was malaligned relative to the atrial septum. As in hearts with atrioventricular concordance and straddling tricuspid valve, where the same septal orientation is found,[2] the connecting node was formed posterolaterally in the right atrioventricular orifice, at the point where the malaligned trabecular septum reached the atrioventricular junction. A regular node at the apex of the triangle of Koch did not give rise to a penetrating atrioventricular bundle.

The second heart studied had absence of the right atrioventricular connection, and in this heart the straddling left valve was committed mostly to the right ventricular chamber, but the rudimentary left ventricular chamber was right-sided and posterior (left-hand pattern ventricular architecture). It is well established that in either situs solitus or with atrial isomerism[13 14] this pattern is accompanied by an abnormal conduction tissue disposition, frequently with a "sling" between two connecting nodes.[15] This was indeed the arrangement found in this particular case, but surprisingly the posterior connecting node was not the regular node in the triangle of Koch. Instead the posterior node was formed in the left atrioventricular orifice, but was again formed at the point where the malaligned trabecular septum made contact with the atrioventricular junction. Thus, it seems that these cases conform with our basic rules for conduction tissue disposition,[16 17] namely that a trabecular septum joining the atrioventricular junction at a point other than the crux and a left-hand pattern of ventricular architecture with situs solitus both presage an anomalous location for the connecting atrioventricular node. The present findings show that this anomalous connecting node cannot only be formed at any point within the right atrioventricular orifice, but also, in patients with solitus atrial chambers, can be formed within the left atrioventricular orifice. As far as we are aware, only Lev *et al.*[18] have previously described a connecting atrioventricular node in the posterior wall of the left atrium. As yet we have not had the opportunity to study histologically hearts with absent connection and straddling valve in which the valve is committed mostly to the left ventricular chamber. In that in all such hearts except one studied grossly in this series the trabecular septum never reached the crux, we anticipate anomalous conduction systems in the majority. Only further histological examination will test the veracity of this prediction, and show what happens when a trabecular septum does extend to the crux.

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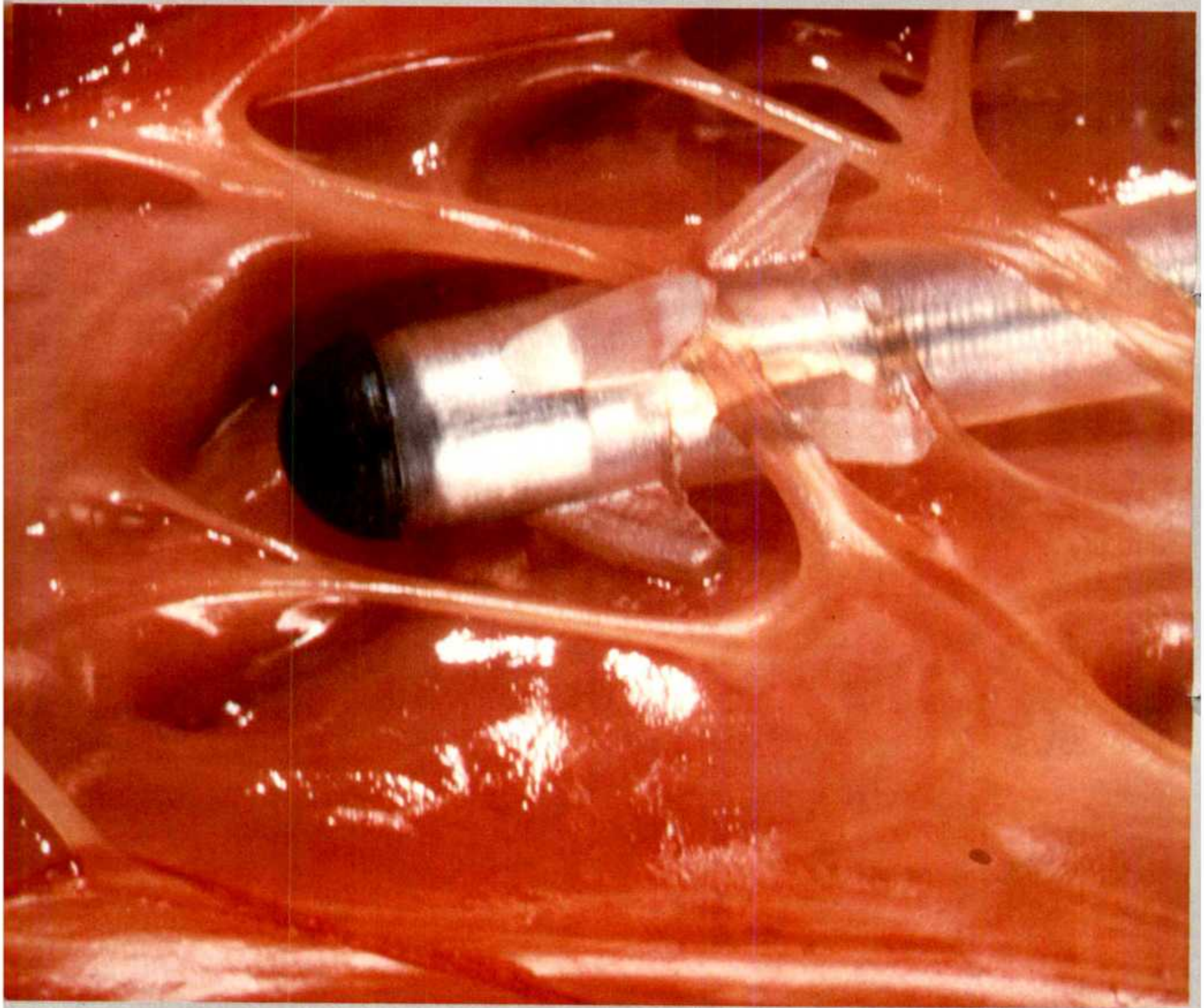

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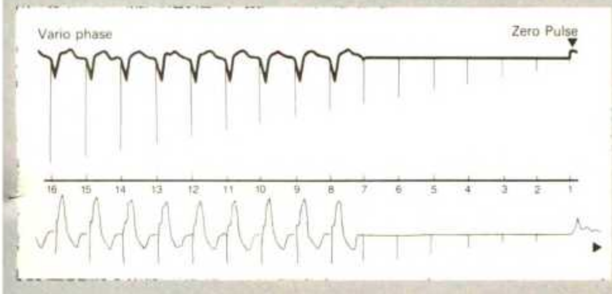

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Br Heart J 1982; 47: 353–6

Serum myoglobin after cardiac catheterisation

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From the Regional Medical Cardiology Centre, Royal Victoria Hospital, Belfast, Northern Ireland

SUMMARY Study of 80 consecutive patients undergoing elective diagnostic cardiac catheterisation showed that after the procedure 25 (31%) developed myoglobinaemia. This was attributed to complications of the catheterisation in two. The remaining 23 had received premedication by intramuscular injection. In patients without intramuscular injections myoglobinaemia did not occur after uncomplicated cardiac catheterisation.

The study did not support the proposition that cardiac catheterisation results in myocardial damage which can be detected by abnormalities of myoglobin but not by conventional indications of myocardial necrosis.

Cardiac catheterisation,[1] and in particular coronary arteriography,[2] have a significant morbidity and mortality; myocardial infarction occurs in a small proportion of patients[3 4] and angina pectoris in a further number.[5] Urinary myoglobin has been measured after routine cardiac catheterisation using an indirect haemagglutination method;[6] it was detected in 39 (27%) of 146 patients.[6] This was attributed to transient and perhaps reversible myocardial injury. All the 146 patients had received premedication by intramuscular injection.

Excretion of myoglobin in the urine was first described after extensive skeletal muscle injury.[7] It has since been found to be a reliable indicator of myocardial infarction.[8 9] Myoglobinaemia has been regarded as a similar indicator.[10] Abnormal amounts of myoglobin in the urine and the serum, however, do not specifically indicate cardiac necrosis, as myoglobin in skeletal muscle is immunologically indistinct from that in the myocardium.[11] Skeletal muscle trauma causes both myoglobinuria and myoglobinaemia.[12 13] It is not clear whether intramuscular injections cause sufficient skeletal muscle trauma to raise the serum myoglobin.[14–16]

In a preliminary study of 35 patients undergoing cardiac catheterisation, myoglobinaemia was detected in nine. It did not occur, however, after uncomplicated cardiac catheterisation in patients who had not had intramuscular injections. A randomised controlled study of 80 consecutive patients was carried out to investigate further the occurrence of myoglobinaemia after cardiac catheterisation.

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Patients and methods

Eighty consecutive patients undergoing elective cardiac catheterisation were studied. The patients were randomised into two groups, so that half received premedication orally, and half by intramuscular injection. The premedicant drug was determined by the physician undertaking the catheterisation. Most patients received 10 mg diazepam (Valium). Some were given 50 mg pethidine and 25 mg promethazine (Phenergan). One received 25 mg pethidine, 6·25 mg chlorpromazine, and 6·25 mg promethazine. Premedication was given one hour before the catheterisation was started.

A venous blood sample was obtained before the administration of the premedication and one, four, eight, and 24 hours after it. Serum creatine kinase was measured in all samples, using an automated method. Serum myoglobin was measured in all samples by radioimmunoassay. Serum aspartate transaminase, lactic dehydrogenase, and blood urea were measured in the first and last samples.

Electrocardiograms were recorded before and after the catheterisation. The contrast medium used in all cases was Urografin 370 (meglumine diatrizoate and sodium diatrizoate). The volume of contrast used and the image intensification screening time required to complete the investigation were recorded.

Any complications that developed during or after the catheterisation were recorded.

DIAGNOSIS AND COMPLICATIONS

Twenty-seven patients underwent left and right heart catheterisation only, 10 right and left heart catheterisation with coronary arteriography, 37 left ventriculography and coronary arteriography, and six left ventriculography only.

Thirty-two patients were found to have coronary artery disease, 32 had acquired valvular heart disease, nine had congenital heart disease, two had hypertrophic obstructive cardiomyopathy, and in five no abnormality was detected.

Five patients developed angina pectoris during coronary arteriography, which was short lasting. One patient developed ventricular fibrillation during arteriography, from which he was rapidly resuscitated. Another patient developed acute obstruction of the left ventricular outflow tract eight hours after catheterisation, and ventricular fibrillation an hour later, from which she was resuscitated.

Results

Twenty-five (31%) of the 80 patients developed myoglobinaemia (>85 ng/100 ml) after cardiac catheterisation. Ten of these had coronary artery disease.

There was no significant association between myoglobinaemia and age, weight, screening time, volume of contrast medium injected, premedicant drug given, performance of a coronary arteriogram, or final diagnosis.

Twenty-three of the 25 patients who developed a raised serum myoglobin after the procedure had had premedication by intramuscular injection. This was very highly significant ($p<0{\cdot}001$). The remaining two patients both orally premedicated had been resuscitated from ventricular fibrillation (Table).

The serum myoglobin was normal in the 23 patients initially. It was raised in 14 (>85 ng/ml) one hour after premedication, before the start of the catheterisation. Four hours after premedication the serum myoglobin was raised in 19. It had returned to normal 24 hours after catheterisation in all.

The distribution of the mean serum myoglobin measurements in those who had received oral premedication is compared in the Figure with that in the patients given premedication by intramuscular injection.

Twenty-three (57·5%) of the 40 patients who had received an intramuscular injection developed myoglobinaemia. None of the 38 patients who had oral premedication and an uncomplicated catheterisation developed myoglobinaemia.

Table *Serum myoglobin in relation to route of premedication*

Serum myoglobin	*Premedication*	
	Oral	*Intramuscular*
Raised >85 ng/ml	2*	23
Normal	38	17

$\chi^2=25{\cdot}658$.
$p<0{\cdot}001$.
*Ventricular fibrillation.

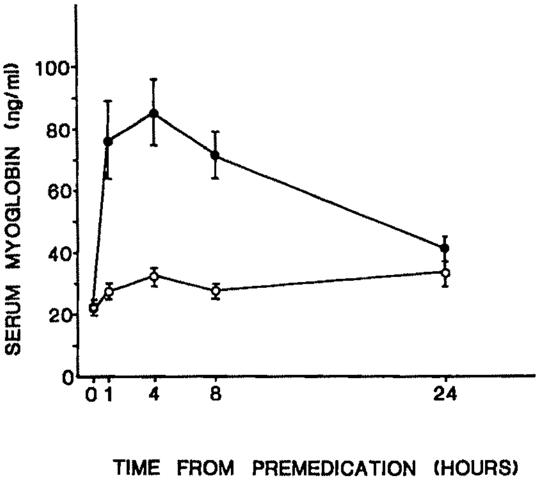

Fig. *Mean (±SD) serum myoglobin measurements in relation to catheterisation. Premedication:* ○ *oral;*
● *intramuscular.*

The serum creatine kinase was abnormal in 20 of the 23 patients who developed myoglobinaemia after intramuscular injection, and in both the patients resuscitated from ventricular fibrillation. It was normal in the remaining patients.

Discussion

Twenty-five (31%) of 80 patients developed a raised serum myoglobin after cardiac catheterisation. Two of these had ventricular fibrillation. The development of myoglobinaemia may have been related to resuscitation. The remaining 23 had had an intramuscular injection. None of the 38 patients who had oral premedication, and who had an uncomplicated catheterisation, developed myoglobinaemia. It was concluded that intramuscular injection of the premedication was the cause of myoglobinaemia in these patients.

No significant relation was seen between myoglobinaemia, the type of procedure undertaken, the screening time required, or the volume of contrast medium injected, all of which might indicate the "severity of the procedure". Nor was there a significant relation with the age, sex, or weight of the patient.

Increase in the serum creatine kinase after cardiac catheterisation was at first attributed to cardiac trauma.[17 18] The finding of an increase in serum creatine kinase, however, was not consistently reported,[19] and it became clear that the observed rise in serum creatine kinase after cardiac catheterisation, in the absence of complications, was the result of skeletal muscle trauma, resulting from intramuscular injection.[20–23] Intramuscular injection can cause an increase in the serum creatine kinase.[24 25] The enzyme rise also depends on the agent injected as injections of physiological saline do not increase the serum creatine kinase.[26 27]

The serum myoglobin appears to be similarly affected by intramuscular injection. Normal serum myoglobin levels have been reported after intramuscular injection of physiological saline.[28 29] Raised serum myoglobin levels have been found in patients receiving daily intramuscular penicillin.[30]

There have been similarly variable reports about the serum myoglobin after cardiac catheterisation. Stone *et al.*[15] reported nine patients who had left ventriculography and coronary arteriography. The serum myoglobin was normal in all before the catheterisation, and in none did it rise outside the normal range in the 24 hours after catheterisation.

This study confirms the development of myoglobinaemia after elective cardiac catheterisation. It attributes the increase in serum myoglobin to the use of intramuscular injections of drugs as premedication, and refutes the proposition that abnormalities in myoglobin after cardiac catheterisation indicate myocardial necrosis.[6]

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Are regions of ischaemia detected on stress perfusion scintigraphy predictive of sites of subsequent myocardial infarction?

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SUMMARY To determine the relation between scintigraphic regions of stress-induced ischaemia and subsequent myocardial infarction, a select group of 21 patients was investigated. Each patient had undergone stress perfusion scintigraphy before myocardial infarction was recorded. After acute infarction, thallium-201 perfusion scintigraphy was performed in 16 patients (76%) and ^{99m}Tc (stannous) pyrophosphate in 14 patients (67%). All patients had at least one post-myocardial infarction scintigram and nine (42%) had both perfusion scintigraphy and infarct imaging.

Nineteen patients (90%) had scintigraphic evidence of stress-induced ischaemia pre-infarction. Scintigraphic regions of infarction were compared with regions of previously demonstrated stress-induced ischaemia. In 11 patients (53%) the myocardial infarction was more extensive; in one of these patients, reimaged one week before myocardial infarction, and in four others (19%) there were matching defects; in three patients (14%) the infarction was less extensive, and in two patients (9%) the infarction was less extensive but also involved regions not previously shown to develop ischaemia. In the final patient (5%) there was no match.

Stress perfusion scintigraphy was generally abnormal before acute infarction in this group of patients. Acute infarction frequently involved regions previously shown to develop stress-induced ischaemia, though these often underestimated the extent of myocardium at risk.

Stress myocardial perfusion scintigraphy has been well documented to be both sensitive and specific to the diagnosis of coronary disease.[1–3] Scintigraphy complements the findings of stress electrocardiography[4 5] and aids the documentation of ischaemia in association with an otherwise uninterpretable electrocardiogram.[6 7] There is little information available, however, regarding the overall predictive value of scintigraphy.

We sought to assess one aspect of scintigraphic prediction—whether by identifying areas of ischaemia stress scintigraphy would also predict the site of any subsequent infarction. To this end we studied a selected group of patients who had previously undergone stress scintigraphy and who had later suffered an infarction with scintigraphy on a second occasion soon afterwards.

Patients and methods

The study population consisted of all 21 patients retrospectively identified to have undergone clinically indicated stress perfusion scintigraphy before a documented myocardial infarction over a six year period at the University of California Medical Center, San Francisco. Each had undergone further myocardial perfusion scintigraphy with thallium-201 (^{201}Tl) or infarction scintigraphy with technetium ^{99m}Tc (stannous) pyrophosphate after infarction, again as clinically indicated. Pre- and post-infarction scintigrams were analysed to compare regions of ischaemia and infarction. There were 15 men and 6 women, with a mean age of 64 years and an age range of 50 to

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77 years. Nineteen patients each had one documented myocardial infarction and two patients had two infarctions during the period between scintigrams. Six events were perioperative and occurred during or within the first week after coronary artery bypass graft surgery. Of the 23 myocardial infarctions, 20 were documented by at least two of the following criteria: (1) a history of prolonged chest pain, (2) the development of new electrocardiographic Q waves of 0·04 second duration or greater, or persistent ST depression and/or T wave inversion, and (3) a rise in the level of serum CK with a positive MB fraction. Three of the perioperative infarctions were additionally confirmed by positive infarct imaging with Tc-99m (stannous) pyrophosphate.

GRADED EXERCISE TREADMILL TESTING

All patients underwent stress perfusion scintigraphy in the fasting state a variable time before the clinical episode of infarction. Cardiac drugs were continued before the exercise study if clinically indicated. Ten patients were on propranolol at the time of stress testing. After giving informed consent, each patient had a standard 12 lead electrocardiogram followed by continuous monitoring with a CM5 bipolar precordial lead early, and by a 12 lead system later in the study period at rest, while standing, with hyperventilation and during maximal treadmill exercise, conducted according to the Bruce protocol.[8] All patients exercised until the appearance of limiting symptoms. In the absence of resting ST-T wave abnormalities a test was considered positive for ischaemia if 1·0 mm or more of horizontal or downsloping ST segment depression compared with baseline, 0·08 second from the J point, developed during exercise or recovery. In the presence of baseline ST-T wave abnormalities as occurred in the setting of left ventricular hypertrophy, left bundle-branch block, and drug effect, the exercise electrocardiogram was considered "non-diagnostic".

MYOCARDIAL PERFUSION SCINTIGRAPHY

Myocardial perfusion scintigraphy was performed in all patients before infarction and in 16 patients after infarction. Stress perfusion scintigraphy was performed after the injection of 2·0 mCi of thallium-201 during peak exercise. Exercise was continued for another 30 to 60 seconds and scintigraphy begun within 10 minutes of completion of exercise. Our imaging technique evolved over the period of the study with the development of the method. Images were obtained in the anterior, 45° left anterior oblique, and left lateral projections early in the study. Later studies included 30° and 60° left anterior oblique projections. Imaging was performed with an Ohio Nuclear Series 120 scintillation camera, using a converging collimator in the early part of the study period, and a high sensitivity parallel hole collimator later. A 20% window was centred at 80 keV. Images were taken to 300 000 counts in the anterior projection, and to equal time in the remaining projections. Patients with abnormal exercise scintigrams returned four hours later for a redistribution study or within a week for a rest perfusion study. Rest perfusion scintigraphy was performed as above, with imaging initiated 10 minutes after radionuclide administration.

Two observers agreed on the interpretation of the original unenhanced analogue images without knowledge of the patient's clinical, electrocardiographic, or angiographic findings. Scintigrams were considered abnormal when relatively decreased perfusion of a region of the left ventricular image was present. Isolated linear apical defects and lone defects of the inferior wall in the left lateral projection are often seen in healthy persons, and so were not considered abnormal. A positive stress perfusion scintigram indicative of exercise-induced ischaemia was defined as a defect in the stress myocardial image not present at rest or redistribution. A positive perfusion scintigram indicative of infarction was defined as a defect in the stress perfusion image which persisted on redistribution, or as a defect in the resting myocardial image.

MYOCARDIAL INFARCTION SCINTIGRAPHY

Myocardial infarction scintigraphy was performed in 14 patients after myocardial infarction. For each study 15 mCi of ^{99m}Tc (stannous) pyrophosphate manufactured according to the method of Huberty and co-workers[9] were administered intravenously and images obtained on Polaroid prints two to four hours later to 300 000 counts in anterior, 45° left anterior oblique, and left lateral projections, using a portable Ohio Nuclear Series 120 of Searle Pho Gamma V scintillation camera with a high resolution collimator. Two independent observers with no knowledge of the clinical history or other laboratory findings agreed on the interpretation of each scintigram.

IMAGE INTERPRETATION

All perfusion and infarct scintigrams were interpreted for regional abnormalities. The regional method of scintigraphic interpretation is shown in Fig. 1. In the anterior projection of perfusion and infarct scintigrams—anterolateral, apical, and inferior regions were identified. In the left anterior oblique projections—septal, inferoapical, and posterolateral regions were identified, and in the left lateral projection—anterior, apical, and inferior regions were evaluated. Regional abnormalities on post-infarction scintigrams were compared with those of scintigraphic stress-induced ischaemia before infarction. A

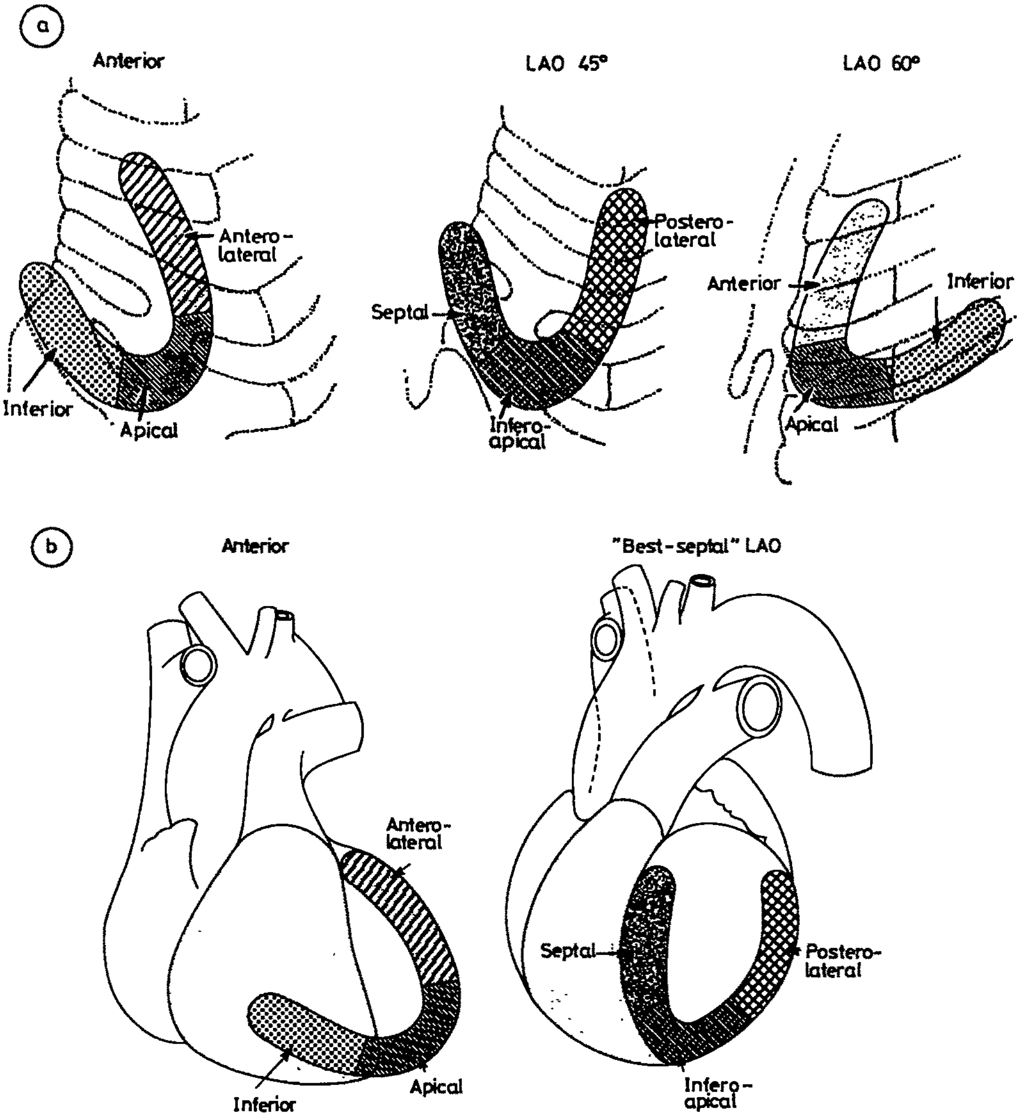

Fig. 1 *Regional methods of scintigraphy interpretation: left ventricular regions. Shown are diagrammatic representations of scintigraphic regions in* ^{201}*Tl perfusion and* ^{99m}*Tc (stannous) pyrophosphate scintigrams used for the assessment of abnormalities. In the anterior projection, anterolateral, apical, and inferior regions are identified. In the left anterior oblique projections, posterolateral, inferoapical, and septal regions are identified. As projections are rotated more laterally, inferior, apical, and anterior regions are identified. Regions are illustrated for anterior, and left anterior oblique 45° and 60° projections.*

post-infarct scintigram was classified as "matching" when scintigraphic abnormalities of myocardial infarction involved the same regions as earlier ischaemia. A post-infarct scintigram was classified as "more extensive" when scintigraphic abnormalities involved all previously ischaemic regions plus any that were previously unaffected or that occurred where there had been no documented ischaemia. A scintigram was called "less extensive" when abnormalities involved some but not all of the previously ischaemic regions, and "less extensive^{+}" if it also involved any previously non-ischaemic regions. A scintigram showed "no match" if the infarct involved regions that failed to correspond to any previously demonstrated ischaemic regions.

Results

A complete summary of results is shown in the Table.

Each of the 21 patients underwent stress perfusion scintigraphy for clinical indications and later suffered myocardial infarction. Two patients, cases 1 and 2, each experienced two myocardial infarctions and one of these, case 1, had two stress perfusion scintigrams, one before the first infarction, the other before the second infarction. One further patient, case 3, had two stress perfusion scintigrams before a single myocardial infarction. After infarction, each patient underwent further myocardial perfusion and/or infarction scintigraphy as clinically indicated. The initial stress perfusion scintigram was performed before myocardial infarction, with a mean time from scintigraphy to infarction of 11·5 months (range one day to 56 months).

All post-infarction scintigrams were performed within four months of infarction. Seventeen post-infarction perfusion scintigrams were performed in 16 patients including one patient, case 1, who was studied before each of two myocardial infarctions. Stress scintigrams with redistribution images were performed in seven of these patients. The mean time from infarction to perfusion scintigraphy was 3·2 weeks, range one day to four months.

^{99m}Tc (stannous) pyrophosphate infarct imaging was performed after infarction in 14 patients. The mean time from infarction to imaging was four days (range one to 11 days). All but two infarct scintigrams were performed within five days of infarction. In these two patients, positive pyrophosphate scintigrams were obtained on days 9 and 11.

All patients had at least one post-infarction scintigram. Nine of the 21 patients had both myocardial

Table

Stress testing				*Scintigraphy*	
Case no.	*Heart rate (% MPHR)*	*ECG*	*Time to myocardial infarction*	*Pre-MI*	*Post-MI*
Classification: more extensive					
1	150 (87%)	±	12 mth	An I	An I S
	150 (87%)	±	4 mth	An S	An Ap I P-L S
2	129 (86%)	+	8 mth	An S	An Ap S P-L
3	147 (98%)	±	14 mth	I	An Ap I S
			32 mth		An Ap I S
4*	78 (52%)	±	37 mth	Ap	Ap
5*	125 (94%)	±	15 mth	Ap S	An-L Ap S
6	130 (71%)	+	7 mth	O	I P-L
7	111 (80%)	±	3 wk	P-L	Ap I P-L
8	114 (76%)	±	10 mth	P-L	Ap I P-L
9	154 (88%)	−	56 mth	O	P-L
10	142 (85%)	−	19 mth	I	I P-L
11	92 (65%)	±	17 mth	S	An Ap I S
Classification: exact match					
4*	42 (30%)	±	1 wk	Ap	Ap
12	107 (61%)	±	16 mth	An Ap I	An Ap I
13	118 (72%)	±	8 mth	An Ap	An Ap
14	131 (85%)	±	23 mth	I P-L	I P-L
15	134 (87%)	+	6 mth	I P-L	I P-L
Classification: less extensive					
16*	145 (90%)	±	3 wk	An Ap I S	An Ap
17	130 (85%)	+	1 d	Ap I P-L	Ap I
18*	122 (82%)	+	4 wk	Ap I P-L	Ap I
Classification: less extensive +					
19*	148 (85%)	+	23 mth	An Ap S	Ap I P-L
20	126 (79%)	±	12 mth	An Ap	Ap — I
Classification: no match					
21*	84 (53%)	±	5 wk	I S	P-L

Abbreviations: MPHR, maximum predicted heart rate; Pre-MI, regions of stress-induced ischaemia before infarction; Post-MI, regions of scintigraphic abnormality after infarction; *, patient experiencing perioperative myocardial infarction; +, positive stress electrocardiogram; −, negative stress electrocardiogram; ±, indeterminate stresss electrocardiogram; An, anterior wall involvement; An-L, anterolateral; Ap, Apical; I, inferior; P-L, posterolateral; S, septal.

perfusion scintigraphy and ^{99m}Tc (stannous) pyrophosphate imaging. Among those who had both myocardial perfusion and infarct imaging, in every case regions of abnormality on infarct scintigraphy corresponded to abnormalities on the rest or redistribution perfusion scintigram.

On stress perfusion scintigraphy before infarction only 10 of the 21 patients attained 85% or more of maximum predicted heart rate. Of the 11 patients who did not reach this level, six were on propranolol. Exercise tolerance was limited by symptoms of pain, fatigue, or dyspnoea and, in one patient (case 4), the second pre-infarct study was limited by the development of complete heart block. Nineteen patients showed stress-induced perfusion abnormalities. Two patients failed to show any abnormalities on stress perfusion scintigraphy. One of these (case 6) attained only 71% of maximum predicted heart rate with a positive stress electrocardiogram while the other patient (case 9) achieved 88% maximum predicted heart rate without significant electrocardiographic changes 56 months before infarction. Both tests were terminated because of fatigue in the absence of chest pain. A third patient (case 4) showed no scintigraphic abnormality when studied initially at 52% of predicted heart rate before infarction but did show an abnormality at a subsequent stress test before infarction. Overall, pre-infarction stress electrocardiograms were positive for ischaemia in six patients, negative in two patients, and indeterminate in 13 patients. One patient (case 6) died two days after infarction. ^{99m}Tc (stannous) pyrophosphate imaging performed one day earlier localised the infarction to inferior and posterolateral regions. This was confirmed at necropsy.

Six patients had historical and electrocardiographic evidence of myocardial infarction before their initial stress perfusion scintigram. In each case it was possible to localise the site of infarction as a nonreversible scintigraphic defect before the postscintigraphic event. These defects were not included in the evaluation of areas of ischaemia or subsequent infarction.

Regions of infarction were more extensive than prior regions of stress-induced ischaemia in 11 patients (Fig. 2). One of these, case 4, when reimaged one week before infarction, and four other cases, showed a match between the extent of scintigraphic infarction and the prior region of stress-induced ischaemia (Fig. 3). Infarction was less extensive than prior regions of stress-induced ischaemia in three patients while in two patients scintigraphic infarction involved only some of the previously noted ischaemic regions as well as other regions not previously shown to be ischaemic. In the final patient, who experienced a perioperative infarction, there was no match between ischaemic and infarcted regions. Of the six patients who failed to achieve an optimal heart rate response while on beta blockers, three showed stress induced defects more extensive than those seen after subsequent infarction.

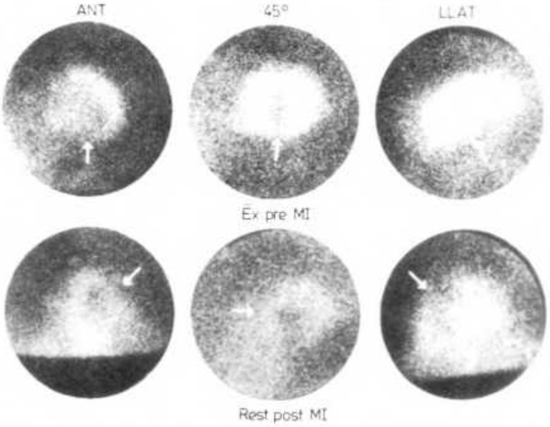

Fig. 2 *More extensive regions of myocardial infarction than prior ischaemia (case 3). In the upper panel (Ex pre MI) are exercise perfusion images in a patient with angina in the anterior (ANT), left anterior oblique 45°, and left lateral (LLAT) projections. Limited inferior abnormalities are marked with arrows in each projection.*

In the lower panel (Rest post MI) are rest images in the same patient after myocardial infarction 32 months later. In addition to the previously recognised inferior abnormalities, anterior (arrow), and apical abnormalities can be seen in the ANT and LLAT projections, and septal abnormalities (arrow), are present in the left anterior oblique 45° projection. This patient showed more extensive regions of infarction than of prior ischaemia.

Discussion

A relatively small, select population was analysed in an attempt to define some aspects of the relation between the abnormalities on stress perfusion scintigraphy and subsequent infarction. While there are many questions that might be addressed regarding this relation, those posed in this study are limited by the nature of the population investigated. The patients studied were unusual in that they were noted to experience an acute myocardial infarction some time after stress perfusion scintigraphy performed during the course of standard clinical follow-up. Each patient underwent subsequent scintigraphic assessment again for clinical reasons. We did not evaluate the clinical course of all patients studied with stress scintigraphy and so cannot comment on the overall incidence of infarction in such patients. Nor could we assess from our data the relative risks for infarction of patients with negative versus positive scintigrams, nor with normal versus abnormal electrocardiograms. While

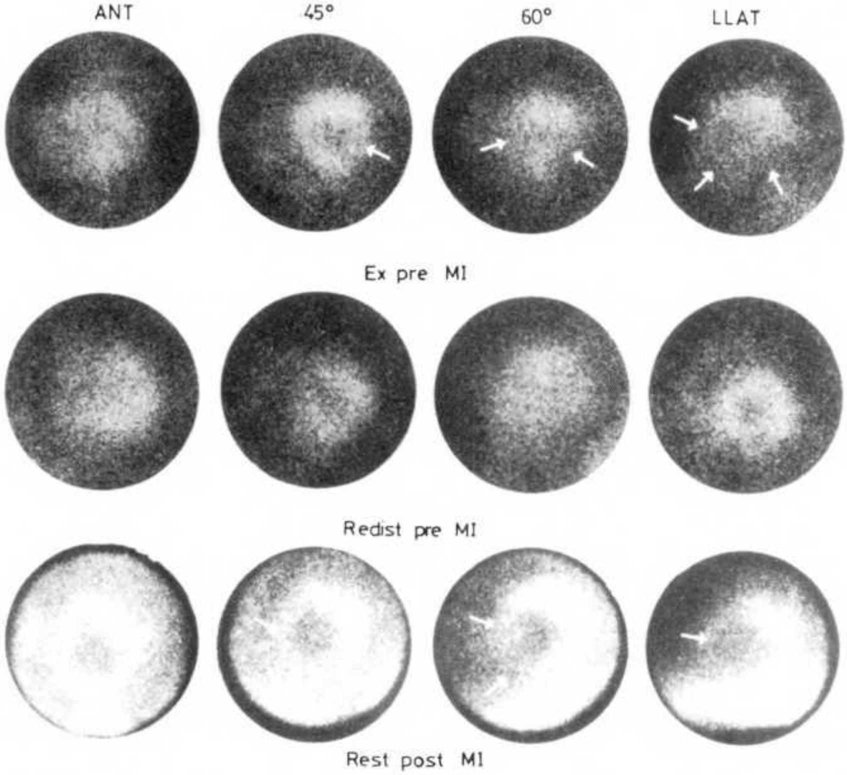

Fig. 3 *Matching regions of myocardial infarction and ischaemia. Shown in the upper panel are exercise perfusion images in a patient with angina. The anterior, left anterior oblique 45° and 60°, and left lateral projections are shown. Posterolateral abnormalities are seen in the left anterior oblique 45° and 60° projections, septal abnormalities in the left anterior oblique 60° projection, and apical, inferior, and anterior abnormalities in the LLAT projections (arrows). The redistribution images show reperfusion of the previously abnormal regions (centre panel). In the lower panel are rest perfusion images in the same patient after myocardial infarction 16 months later. The left ventricular cavity appears enlarged. Septal, inferior, and posterolateral regions of the left anterior oblique 45° and 60° projections, and the inferior, apical, and anterior regions of the LLAT projection are abnormal (arrows). These regional abnormalities match those identified before infarction. Abbreviations as for Fig. 2.*

positive stress electrocardiograms are known to be related to many times greater risk of coronary events than are negative stress electrocardiograms,[10] determination of the prognostic significance of stress scintigraphy requires a long-term evaluation of large populations. The population studied here, however, was an unusual one and was chosen based on the performance of scintigraphy in patients with confirmed infarction and earlier stress scintigraphy. With this population, some important observations can be made particularly regarding the relation between localisation of reversible ischaemia and subsequent regions of myocardial infarction.

Myocardial stress perfusion scintigraphy was generally abnormal in patients who suffered myocardial infarction within 32 months. While stress electrocardiography was less useful and only positive for ischaemia in six patients or 29% of those studied here, many patients presented with indeterminate electrocardiographic findings which were often the initial indication for scintigraphy. Myocardial infarction generally involved regions of previously demonstrated ischaemia. In 18 of 19 patients with positive stress perfusion scintigraphy, the regions of infarction corresponded with some or all of those previously shown to be ischaemic. Regions of stress-induced ischaemia, however, often underestimated regions of subsequent infarction in the group as a whole.

The subgroup of six patients who had perioperative myocardial infarctions presented a spectrum of findings. Among these was the only patient in the series to show no anatomical match between an area of stress-induced ischaemia and the region of subsequent infarction. This suggests that the infarction occurred in an area not previously noted to become ischaemic but spared an area which had previously become ischaemic. Such might be the case, for example, if revascularisation aided previously ischaemic regions but surgery provided no benefit or reduced perfusion in a less severely affected bed, probably perfused by a stenotic vessel, but not previously associated with ischaemia.

In other cases regional infarction appeared to involve the area of earlier ischaemia to a greater or lesser extent. Frequently areas of infarction involved regions beyond those noted to be ischaemic, consistent with the previously noted hypothesis that perfusion scintigraphy does not identify the full extent of myocardium at risk.[4 11 12] Such underestimation may be the result of the relative nature of stress perfusion scintigraphy itself. It has been established that scintigraphic global sensitivity for coronary disease detection is greater than regional sensitivity and the method can generally detect approximately 50% of involved vessels.[11 12] Thereby, only the most severely diseased vessels are likely to produce recognisable defects. New methods employing radial analysis of washout data may help to identify such areas at risk.[13] There is also no reason to believe that all regions distal to a significant lesion become ischaemic at stress for much depends on the level of stress achieved. Alternatively, underestimation of the region of subsequent infarction may relate to the underestimation of the amount of myocardium at risk. Massie and co-workers[11] and others[14] have shown that the ability to demonstrate a region of stress-induced ischaemia is significantly related to the level of stress. Not all patients achieved a satisfactory level of exercise. It is likely that with higher levels of exercise, scintigraphic evidence of further regions of ischaemia would be apparent. Furthermore, progression of coronary disease between initial scintigraphic study and subsequent infarction may in part explain this disparity. Infarction involving only a part of the region previously noted to be ischaemic could similarly reflect infarction in the area of a distal or branch vessel rather than the main stem which gave rise to the larger ischaemic zone. It could alternatively indicate the interim development of collateral vessels and a margin of protection or the inability of the post-infarct scintigram to identify regions of subendocardial involvement.

Although two of the three negative stress scintigrams obtained before infarction were associated with a suboptimal stress and heart rate response, the level of stress achieved did not appear to affect the relation between the extent of scintigraphic ischaemia and subsequent infarction. In addition, the interval between stress scintigraphy and infarction did not affect this relation.

Collateral vessels have been said to affect the sensitivity of stress evaluation.[15] The influence of collaterals on scintigraphic abnormalities was evaluated in the seven patients who suffered perioperative infarctions and had undergone angiography before surgery. All these patients had triple vessel disease and six showed evidence of collateral circulation. In this small group of patients the presence of collateral circulation did not appear to influence the distribution of scintigraphic regions of ischaemia or subsequent infarction. The one patient without collaterals was the only patient in the series with disparate regions of ischaemia and infarction, suggesting that the scintigraphic findings could relate to the isolated nature of the affected bed.

Although all patients had myocardial scintigraphy after infarction, not all had repeat myocardial perfusion scintigraphy, as five patients had only ^{99m}Tc (stannous) pyrophosphate infarct imaging. Though previous studies using a comparison of both radiotracers in patients with acute infarction have shown some minor discrepancies when comparing the size of involvement, the studies generally agreed on the region of involvement,[16 17] as did each of our studies in the nine patients assessed here by both methods.

Although preliminary, the study confirms the expectation that thallium stress perfusion scintigraphy is generally abnormal in patients who subsequently suffer myocardial infarction and that regions of infarction tend to involve those of demonstrated ischaemia. The latter often underestimate the region of subsequent infarction. The study population is a relatively small select patient group which prohibits overall conclusions regarding the risk of findings on stress perfusion scintigraphy for subsequent infarction and other aspects of prognosis. The data presented, however, constitute initial observations on the relations between the incidence and extent of perfusion scintigraphic anormalities and subsequent infarction. A prospective study involving a larger population is needed to obtain more qualitative and quantitative data regarding this relation, an important one for assessing the prognostic significance of the scintigraphic estimation of ischaemic myocardium.

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Coronary bypass for acute rest angina
10 year follow-up

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SUMMARY We followed up for 6·5 to 10·3 years 100 consecutive patients who had had coronary bypasses (1·8 per person) for acute angina at rest. There was a mean of 2·1 coronary stenoses per person. Mortality rates were 1·4% per postoperative year, or 2·2 times that of normal subjects of the same age. Angina was usually satisfactorily relieved but severe recurrences, mainly from late graft closure, required reoperation in 20 patients. Life style has been preserved; and 91 resumed work, with 52 at an average age of 61 years continuing to work eight years later. Better results than these may be obtained from the improved diagnostic and therapeutic methods of the 1980's.

Early reports of bypass surgery for acute coronary insufficiency indicated that a pronounced relief of angina could be obtained at a mean cost of 8% hospital mortality.[1–6] The subsequent course up to 10 years after such operations has been described in a single report. The survivors had a relatively low mean yearly mortality of 3%, the prevalence of angina rose from 19% at one year after operation to 53% at five years, and those patients with better treadmill tolerance had significantly fewer acute coronary events.[7]

Our first 100 patients undergoing urgent bypass had a total operative mortality of 0·8%, comparable to that of many centres today. We present their follow-up course to 10 years. We found that 89% of patients were alive and 84% of them had class I or II effort tolerance a mean of 7·8 years after operation; this supports the growing view that revascularisation of unstable anginal states can have enduring benefits at acceptable costs. The palliative nature of the procedure was shown by the fact that 20 patients required a second operation an average of 3 years after the first.

Subjects and methods

Patient selection, treatment, and five year postoperative course have been previously described.[8] In summary, 125 consecutive patients admitted to hospital between June 1970 and March 1974 for typical severe acute rest angina which had begun to occur spontaneously within the previous month were subjected to early coronary arteriography by the Judkins technique. Patients over the age of 70 years, those with signs of transmural infarction within one month or congestive failure, and those with other severe complicating disease, such as malignancy were excluded. Of the 125 patients, 10 had no critical coronary lesion and 15 had diffuse coronary and/or ventricular disease, so they were judged not to be surgical candidates. The remaining 100 surgical cases each had a mean of 2·1 stenoses greater than 70% of the luminal diameter in major arteries. An abnormality of left ventricular contraction was seen on angiography in 79 cases. None died or infarcted while awaiting coronary arteriography, but one had a nontransmural infarction during the procedure. In no case was beta blockade or balloon assist pumping used before operation.

Bypass operations (mean 1·8 grafts per patient) were performed, usually within 24 hours after arteriography, by senior surgeons using standard techniques in 99 patients. One patient with anterior descending coronary disease was explored but could not be bypassed.

All patients have been followed biennially until the autumn of 1980. Most were examined, but some were only contacted by telephone. Supplementary information was obtained from personal physicians and from hospital records.

Results

A worth-while surgical result with substantial or complete relief of angina was judged to have been obtained in 97 of the 100 patients. Of the remaining three patients, one had a large myocardial infarction

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during the night between angiography and surgery, and never recovered from the ensuing low output state, dying three months later. A second patient had an exploratory thoracotomy only. The third case was found to have severe left coronary spasm without a fixed stenosis, resulting in graft closure with recurrent rest angina; this was the only recognised case of symptomatic vasospasm in the study.

Of the 100 patients, 89 were alive at the end of the follow-up period. Their clinical status is summarised in the Table. Seventy-five were leading active lives, having NYHA class I or II effort tolerance. Ninety-one had returned to work, and 52 were still working at the last follow-up; 18 of those who had stopped working had retired after their 65th birthday, and only nine of the total of 89 patients were disabled by heart disease. Thirty-five had had no further angina or effort intolerance since operation.

The incidence of angina postoperatively was 33% at 2 years, 37% at 5 years, and 52% at 7·8 years. This symptom reached class III or IV severity at various intervals after operation in 35 patients. Failure of adequate response to nitrates and/or propranolol led to a second operation in 20 cases with one death resulting from bleeding of uncertain cause. Of the 19 survivors, 14 experienced an improvement in angina to class I or II. Two patients who had a third bypass procedure survived.

Coronary arteriographic findings in the 20 patients who underwent a second operation included graft closure alone in eight cases, progression of native arterial disease in two; and both in 10. The principal type of graft replaced was saphenous vein in 14 (of the total of 130 inserted initially), internal mammary artery in one of 34, and radial artery in three of 16. An average of 1·7 grafts was inserted at the second operation. The interval between the first and the second operations was less than one year in five patients and greater than five years in seven, and averaged three years.

Episodes of late acute coronary insufficiency with or without myocardial infarction or congestive failure were observed in 30 patients, a rate of 3·6% per postoperative year.

Table *Clinical status of 89 patients eight years after urgent coronary bypass*

Age: 42–78 years	Average: 61·1 years
Male sex	75 patients
Angina free	43 patients
NYHA Class I	52 patients
NYHA Class II	23 patients
NYHA Class III	14 patients
NYHA Class IV	0 patients
Working	52 patients
Disabled by heart disease	9 patients
Retired ≥ age 65 years	18 patients
Reoperated	18 patients

Eleven of the 100 patients died at intervals from 0·3 to 7·5 years postoperatively, averaging 3·7 years. Their ages averaged 63 years at death. Heart disease accounted for deaths in seven cases, cancer in three, and one died accidentally. The survival curve by life table method, compared with an age and sex adjusted normal series, is presented in the Fig.[9]

Discussion

The principal accomplishments of revascularisation in these 100 patients appear to have been three: pronounced relief of angina in 97; improvement in effort tolerance by 2 or 3 NYHA classifications in 87; and a possible prolongation of life in the group as a whole, with 89 patients being alive an average of 7·8 years after operation.

The postoperative improvement in 97 of 100 patients was attended by return to work in 91, 52 of whom were working an average of 7·8 years later. Apart from the personal satisfaction of resuming an active life, the economic benefit from the operation may be illustrated by the fact that the total earnings of this group after operation was approximately eight times the cost of their professional and hospital care, a figure unlikely to have been achieved without operation, as half of the group would probably have continued to suffer class III or IV angina.

A contrasting experience reported by Russell *et al.*[10] showed a lower rate of return to work in patients with unstable angina, with 54% of those randomised to medical treatment and 44% of those to bypass surgery employed approximately 12 months later. The crossover of one-third of the medical group to surgery did not increase their employment rate. Proudfit *et al.* noted that 37% of men with medically treated coronary disease were still working 10 years after arteriographic diagnosis.[11]

To what factors may one attribute the generally favourable course of the present cases? First, patients with severe ventricular disease, including acute transmural infarction or congestive failure or diffuse coronary lesions, were with two exceptions not offered surgery. Second, the bypass operations were done only by experienced surgeons who achieved the unusually low mortality rate of 0·8% at a time when reported rates averaged more than 5%. This low figure implies expert myocardial preservation and graft construction, such as those widely achieved at the present time. Third, the operation consisted of a single bypass graft in 35 patients, though 12 of them had 50 to 65% stenosis of a second major artery that nowadays would be grafted and which should have had an adverse effect. Fourth, considerable attention

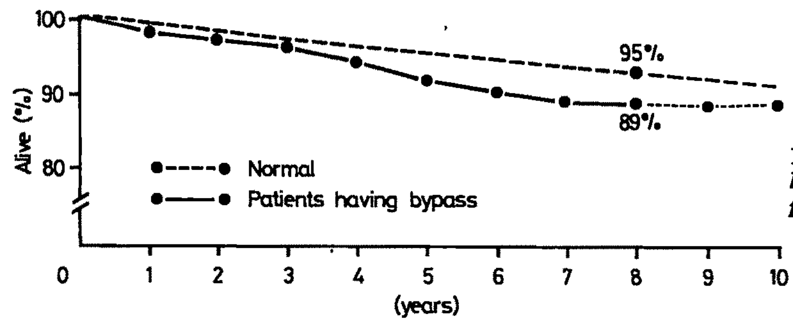

Fig. *Life table survival of 100 patients having bypasses compared with general population of same age (54 years).*

was paid to postoperative care with follow-up care by the cardiologist and surgeon as well as by the personal physician.

Our management procedure for patients with unstable angina was developed in 1970 and differs in some respects from the current widely accepted one.[12–14] The latter advocates giving nitrates, beta blockers, and/or a calcium inhibitory drug for various periods. Coronary arteriography is deferred for some days in those who quickly become symptom free and often for a longer period when stress electrocardiography shows a good exercise tolerance or when patients seem physically or emotionally unsuited for surgery. Arteriography is done usually on day 3 or 4 in those patients who have severe recurrent pain after optimal medical management has been achieved over a 24 to 48 hour period, as these high risk cases have a poorer prognosis[15] and a higher incidence of significant coronary stenosis.[12] The demonstration of critical left main, double, or triple coronary disease leads to bypass surgery within a day or two in the high risk cases and to a conveniently scheduled operation in the others. Thus, three to five days elapse between admission to hospital and operation in high risk individuals and four days to a week or more in patients who respond to medical treatment. While this deliberate management plan has the advantages of more thorough patient evaluation and care and of convenient scheduling of procedures, it has three principal shortcomings: (1) It is associated with a death rate in hospital of about 3% and a myocardial infarction rate of 5 to 9% in the medically treated groups, including those in whom surgery is planned; (2) recurrent angina in one-third of cases treated medically after early pain relief results in operation being necessary later after increased aggregate suffering and expense; (3) effort intolerance and severity of residual angina are greater at least during the first two years of follow-up in most patients treated by medical means alone.

We suggest a modified management plan in the light of the present report to attempt to counter these drawbacks. The first 12 to 24 hours in hospital consist of intensive medical treatment with repeated clinical assessment, including electrocardiograms during pain. Patients who then appear free of serious complicating disease and who are favourably disposed towards having surgery are offered coronary arteriography whether or not the pain has subsided, as its pathological cause remains and may progress. The two-thirds of this group who are found to have one or more large segments of ventricle with jeopardised function, and greater than 70% fixed stenosis of two or more large coronary arteries, undergo bypass grafting usually by the third day in hospital. This advice assumes that the risk of surgical mortality is under 2%, a figure now widely achieved. The management of the patient with a single vessel stenosis or with severe ventricular damage and/or distal vessel disease remains unsettled, and judgment in the individual case may await demonstration of refractoriness of the angina to medical treatment. This regimen is designed to effect optimal relief of the severe acute coronary insufficiency that can be confirmed arteriographically in approximately 90% of patients with severe unstable angina; it is not merely an attempt to qualify them for surgical treatment. It avoids operating on this type of patient as an emergency within 24 hours of admission, a practice that has been shown to increase the risk of death to 4%, and in particular of perioperative myocardial infarction to 17%, by one experienced group during the 1970–76 period.[16] Newer methods of treatment such as percutaneous transluminal coronary angioplasty[17] or the infusion of lytic agents[18] in the unusual case of fresh coronary thrombosis[19] may be useful in some patients.

The palliative nature of the bypass operation is exemplified by the progressive return of angina postoperatively in most cases, both in Davidson's[7] and in 65% of our series. The apparent basis for this symptomatic deterioration is narrowing of the graft(s) and to a lesser degree of the native coronary arteries, processes that at present appear to be not particularly amenable to treatment.[20] The recurrence rate of such stenoses in our patients can only be estimated, since repeat coronary arteriography was done only in those who had severe symptoms. In the latter, this nearly always showed a critically ischaemic area, which in 19 of the 20 patients was successfully revascularised with renewed relief of angina in 14. When repeat coronary arteriography was done routinely in 100 coronary patients bypassed in the early 1970's, Campeau *et al.* found a mean annual vein graft closure rate of 2·1% between the first and sixth year after operation.[21]

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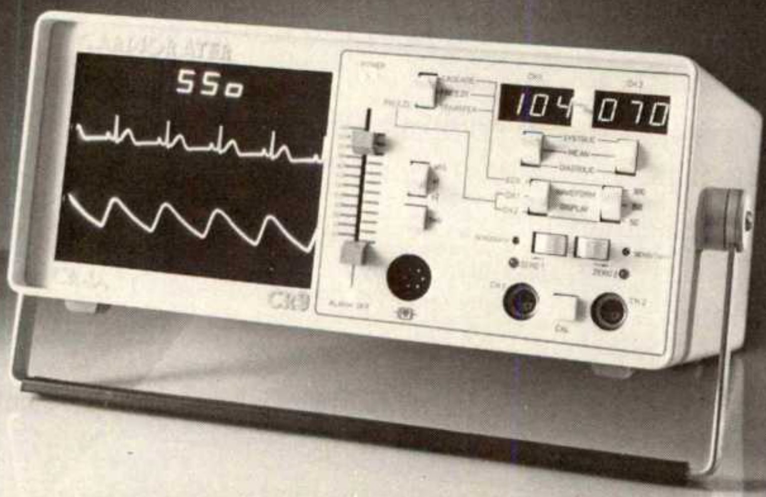

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Br Heart J 1982; **47**: 369–74

Continuous coronary sinus and arterial pH monitoring during pacing-induced ischaemia in coronary artery disease

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From the Cardiothoracic Institute and National Heart Hospital, London

SUMMARY Catheter tip pH electrodes were used for continuous recording of coronary sinus and arterial pH during atrial pacing in 20 patients undergoing coronary arteriography for chest pain. An ischaemic response to atrial pacing was identified by the onset of angina and/or electrocardiographic abnormalities. Technically satisfactory coronary sinus recordings were obtained in 18 patients. Mean coronary sinus pH at the peak pacing rate fell by 0·021±0·006 units (n=9) in the ischaemic group, while there was no significant change in the non-ischaemic group. A larger fall in coronary sinus pH (−0·052±0·009) was found in the ischaemic group in the 30 seconds *after* the end of atrial pacing, the maximum change occurring after 16·1±1·5 seconds. A maximum fall of coronary sinus pH>0·02 units identified patients with an ischaemic response. Changes in arterial pH did not account for these results. The sensitivity of coronary sinus pH recording for the detection of ischaemic heart disease is enhanced by sampling during the "washout" phase after the end of pacing.

Although atrial pacing has been widely used clinically in biochemical studies of myocardial ischaemia,[1 2] many reports have indicated a poor correlation between changes in coronary sinus lactate concentration and the development of angina pectoris or ischaemic electrocardiographic abnormalities.[3 4] Recent studies of regional coronary flow during pacing-induced ischaemia may explain the small changes in lactate concentrations which often occur. In an area of myocardium distal to a critical coronary stenosis, not only is there no *increase* in coronary blood flow to meet the increased metabolic demands induced by tachycardia, but there is an absolute *fall* in coronary flow.[5 6] Reduced arterial flow in an ischaemic area causes retention of the end product of anaerobic metabolism in the tissue, and such metabolites as are washed out will be considerably diluted by the increased coronary venous effluent from non-ischaemic myocardium. At the end of pacing the increased flow through the non-ischaemic myocardium falls to normal within seconds[7] and there is a rapid increase in flow to the ischaemic area.[6] A "washout" of metabolites coupled with reduced dilution by non-ischaemic venous effluent may result in larger changes in coronary sinus metabolite concentration in the first few minutes after cessation of atrial pacing.

Continuous measurement of coronary sinus lactate is not possible, and we have therefore used specially designed catheter tip pH electrodes[8] to record arterial and coronary sinus pH continuously during and after atrial pacing. The hydrogen ion is of particular interest since tissue acidosis is a possible cause of reduced myocardial contractility in acute ischaemia.[9]

Methods and subjects

PH ELECTRODES

The construction and evaluation of the catheter tip pH electrodes have been described in detail.[8] The pH electrode is mounted on the tip of a fine polyethylene tube, which can pass through the lumen of an 8 French gauge Cournand catheter. The electrodes were sterilised in aqueous glutaraldehyde and were calibrated before and after all studies to ensure no loss of function had occurred.

Twenty patients with effort related chest pain

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already scheduled for routine coronary arteriography were studied. There were 17 men and three women. The age range was 37 to 63 years. Patients with recent myocardial infarction, rest pain in the previous week, arrhythmias, or bundle-block were excluded. Informed written consent was obtained in all cases. Sixteen of the patients underwent a treadmill exercise test with 12 lead electrocardiographic recording before catheterisation.[10] The leads in which abnormalities occurred were noted.

PROCEDURE OF PACING TEST

After an overnight fast, the patients were premedicated with diazepam 10 mg intramuscularly. Beta-blockers and calcium antagonists were withdrawn the day before catheterisation, and no patient was taking digitalis. The coronary sinus was cannulated from a left antecubital vein, and the tip of the catheter sited halfway between the coronary sinus ostium and the left heart border. Cannulation was confirmed by injecting radiographic contrast down the Cournand catheter around the pH electrode. The pH electrode tip was then gently advanced 1 cm out of the distal end of the Cournard catheter. The reference electrode (Radiometer, Copenhagen, K4112) was connected to the line flushing the Cournard catheter with heparinised saline. The output of the pH electrode was allowed to stabilise.

A second operator performed a right brachial arterial and venous cutdown to introduce a NIH catheter to the left ventricle and a bipolar pacing electrode to the high right atrium. The patients were heparinised (100 units/kg) after catheter insertion. In nine patients, after baseline left ventricular pressures had been obtained, the NIH catheter was replaced by a second Cournand pH electrode catheter. The tip of this electrode was sited in the right axillary artery distal to the origins of the carotid and vetebral arteries. A pressurised flushing system (Intraflo, Sorenson Research, Salt Lake City, USA) was used for the arterial pH electrode, and a separate reference electrode connected. The amplifiers for the arterial and coronary sinus pH electrodes were operated in differential mode, and were "earthed" to the patient's right leg.

Atrial pacing began when baseline pressure and electrocardiograms had been recorded, and the outputs from the coronary sinus and arterial pH electrodes were stable. Left ventricular pressure, electrocardiogram (leads I, II, V5), and pH were recorded continuously. Atrial pacing started at 90/min. The rate was increased by 10 beats/min at one minute intervals up to a maximum rate of 180 beats/min, or the highest rate at which 1:1 atrioventricular conduction continued. If the patient complained of angina pectoris, or the electrocardiogram showed ST segment depression of 2 mm or more, pacing was discontinued after the one minute at that rate had been completed. After cessation of pacing, pH, pressure, and electrocardiogram were recorded for a further three minutes. At the end of the pH recording, the position of the electrode was checked once more by the injection of radiographic contrast. Left ventriculography and coronary arteriography were then performed.

The changes of arterial and coronary sinus pH from the values at the onset of pacing were measured. Results were expressed as mean±one standard error of the mean, and analysed by Student's t test or the χ^2 test.

Results

CLINICAL RESPONSE TO PACING

Atrial pacing studies were performed on 20 patients. Two groups were defined by the clinical and electrocardiographic response to pacing.

(1) *Non-ischaemic group* (n=10)

Four patients had normal coronary arteries or <50% reduction in vessel diameter on coronary angiography. All had negative exercise tests and, apart from one patient with atypical chest pain before pacing, there was no angina or electrocardiographic abnormality during or after the pacing test.

Significant coronary artery disease (>50% stenosis in one or more vessels) but no angina or electrocardiographic abnormalities on pacing were present in five patients. Three of these patients underwent an exercise test, and developed angina and diagnostic ST segment depression. None of the patients could be paced at a rate adequate to induce angina owing to the development of atrioventricular block. The failure to induce ischaemia in these patients is consistent with previous studies which showed that significantly higher heart rates are necessary to produce angina by pacing than by exercise.[11]

One patient had severe right coronary artery disease and a normal left coronary artery. The venous effluent from the ischaemic area was shown on coronary arteriography to enter the coronary sinus close to its ostium, and therefore acid efflux could not be recorded by our technique.

These 10 patients comprised a "non-ischaemic group" in terms of the response to atrial pacing.

(2) *Ischaemic group* (n=10)

Ten patients had significant left coronary disease with pacing-induced angina and/or diagnostic ST segment depression on the electrocardiogram. Nine of these patients underwent exercise testing. All developed angina, with diagnostic electrocardiographic abnormalities in eight out of nine. These patients comprised an "ischaemic" group.

CHANGES IN CORONARY SINUS AND ARTERIAL PH

Of the 20 patients studied, 11 had coronary sinus pH recording alone, and in nine simultaneous arterial and coronary sinus recording was attempted. Simultaneous recording proved to be technically more difficult as a result of electronic interference. Of the nine simultaneous tracings, two coronary sinus and one arterial tracing were rejected as technically unsatisfactory, leaving a total of 18 coronary sinus and eight arterial tracings for analysis, divided equally between the ischeamic and non-ischaemic groups.

The coronary sinus pH tracings from two patients, one with an ischaemic response to pacing and one without angina or electrocardiographic abnormalities, are illustrated in Fig. 1. Fig. 2 shows the pooled data for the coronary sinus pH response in the two groups. The pH changes before pacing, in the last 120 seconds before the end of pacing, and the 180 seconds after restoration of sinus rhythm are shown. During pacing there was a fall in coronary sinus pH in the ischaemic group (that is an acidosis) which reached −0·021±0·006 pH units (n=9) (p<0·01) at the end of pacing, and was significantly different (p<0·005) from the mean value in the non-ischaemic group (+0·007±0·005 pH units, n=9). After pacing, no significant change in coronary sinus pH occurred in the non-ischaemic group, while in the ischaemic group mean pH fell in the first 10 seconds from −0·021±0·006 to −0·039±0·006 (p<0·001, paired t test). The mean maximum change in the ischaemic group was −0·052±0·009 which was significantly greater than the value obtained at the moment pacing ended (−0·021±0·006, p<0·001, see Fig. 4). The maximum fall in coronary sinus pH occurred at slightly different times in the 30 seconds after pacing was terminated (mean 16·1±1·5 seconds from the end of pacing). Coronary sinus pH in the ischaemic group returned gradually towards control in the 180 seconds after pacing, while no further change occurred in the non-ischaemic group (Fig. 2).

In Fig. 3 is shown the coronary sinus pH response in the ischaemic group (n=9), together with the simultaneous arterial pH recordings (n=4). The changes in coronary sinus pH cannot be explained on the basis of a parallel change in arterial pH. A slight arterial alkalosis developed with the onset of ischaemia, presumably because of hyperventilation.

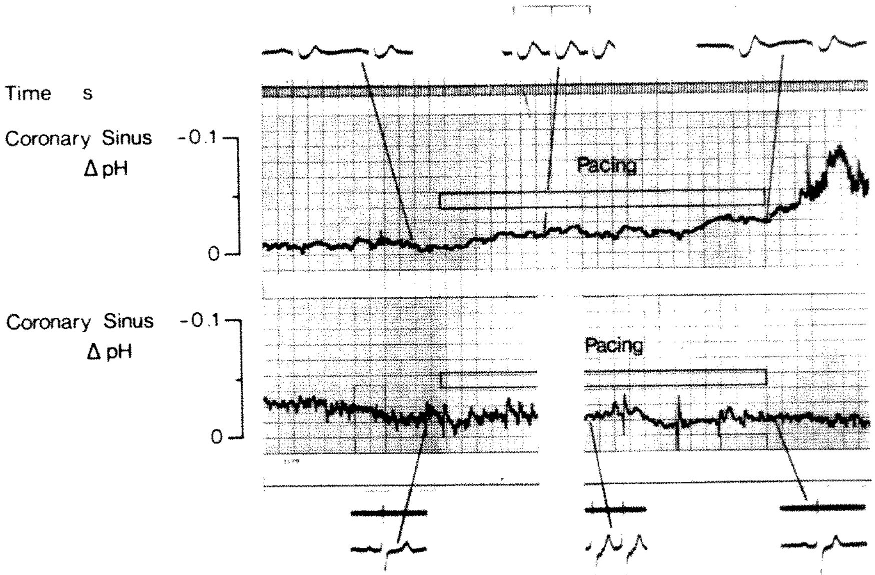

Fig. 1 *Continuous coronary sinus pH recordings from two patients before, during, and after atrial pacing. Upward deflection indicates acidosis.* Upper: *a typical ischaemic response in a patient who developed angina and ST depression after two minutes pacing. A small fall in coronary sinus pH occurred during pacing, but a much larger fall was demonstrated after cessation of pacing. The maximum fall occurred 25 seconds after the end of pacing.* Lower: *the patient was paced at incremental rates up to 170/min with no angina or electrocardiographic abnormalities. The tracing is interrupted and shows the first 30 seconds and last 60 seconds of pacing, with pre- and post-pacing recording of pH. No change in coronary sinus pH occurred during or after pacing.*

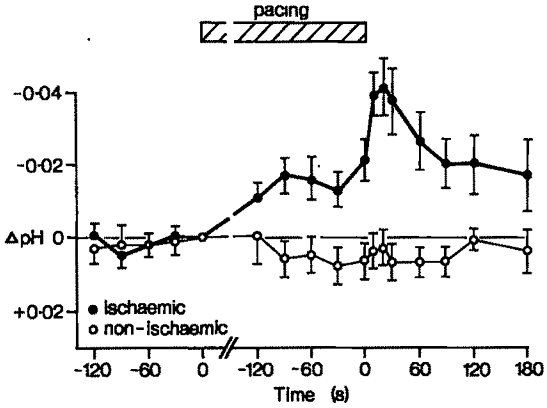

Fig. 2 *Mean change in coronary sinus pH for 120 seconds before the onset of pacing, the last 120 seconds of pacing, and 180 seconds after the end of pacing, in the ischaemic and non-ischaemic groups. Results are expressed as changes in pH from the value at the onset of pacing, upward deflection indicating increasing hydrogen ion concentration (fall in pH). In the ischaemic group, a significant coronary sinus acidosis occurred during pacing, but the maximum change was seen 20 seconds after the end of pacing. No acidosis occurred in the non-ischaemic group (n=9 each group).*

This resulted in a widening of the mean arteriocoronary sinus pH difference by 0·04 pH units at the end of pacing and by 0·06 units, 20 seconds later. It should be emphasised that no significant change in arterial pH occurred in the 60 seconds after pacing, indicating that the prompt fall in coronary sinus pH after pacing must be the result of efflux of hydrogen ions from the myocardium rather than any arterial pH change. Arterial pH in the non-ischaemic group did not differ from the control value before, during, or after pacing.

The individual values for coronary sinus pH at the end of pacing were compared with the most acidic value obtained in the first 30 seconds after pacing in both the ischaemic and non-ischaemic group (Fig. 4). At no time did coronary sinus pH in the non-ischaemic group fall by greater than 0·02 units below the value at the onset of pacing. At the moment pacing ended, five out of nine patients in the ischaemic group already had changes greater than $-0{\cdot}02$ in coronary sinus pH. All but one patient in the ischaemic group subsequently showed a maximum fall of greater than 0·02 units in the 30 seconds after switchoff. Apart from this one patient a positive pH response (maximum change $-0{\cdot}02$ units) discriminated between patients with and without myocardial ischaemia as assessed from the electrocardiogram and the onset of chest pain ($\chi^2=11{\cdot}4$, $p<0{\cdot}001$ for all patients). The discrimination was greatly improved by using the maximum fall in pH in the 30 seconds after pacing, rather than the value at the end of the pacing period.

Discussion

The results presented above show that pH recording from the arteries and coronary sinus of man is technically feasible with catheter tip electrodes. Continuous recording of pH permits identification of rapidly occurring changes in hydrogen ion concentration which would be missed by conventional sampling techniques. We have verified that acidosis does develop in the ischaemic myocardium of man and that a more pronounced change in coronary sinus pH occurs immediately *after* the end of pacing than *during* pacing itself. Tissue acidosis in the myocardium is an important cause of contractile failure during ischaemia.[9]

In the presence of normal coronary arteries, pacing-induced tachycardia results in an increase in myocardial oxygen and substrate demand which is balanced by a parallel increase in coronary flow.[12, 13] This increase must occur as a result of vasodilatation, since the diastolic pressure/time index steadily falls with increasing heart rate.[14] Even at very rapid heart rates, however, the capacity for vasodilatation is not exhausted[15] and no evidence of subendocardial ischaemia is found.[16]

In the presence of coronary artery stenosis, the capacity for distal vasodilatation may initially allow a small increase in coronary flow through a stenosis. As

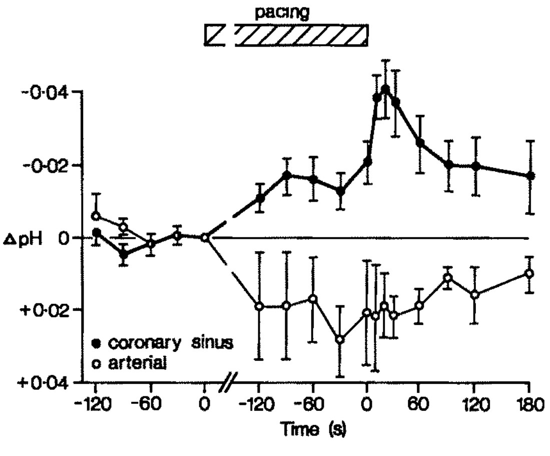

Fig. 3 *Mean changes in arterial and coronary sinus pH in the ischaemic group before, during, and after atrial pacing. A mild alkalosis developed in the arterial blood, which in conjunction with the coronary sinus acidosis produced an increase in arteriovenous pH difference. No significant change in arterial pH occurred after the end of pacing in contrast to the rapid fall in coronary sinus pH. n=9 coronary sinus tracings, n=4 arterial changes.*

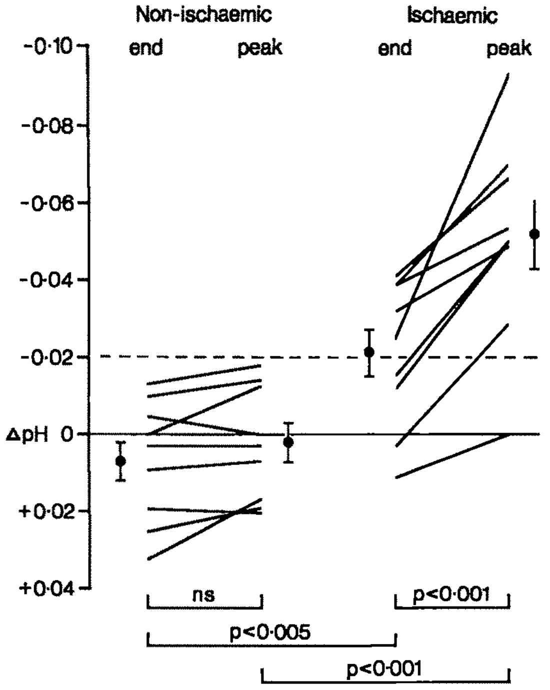

Fig. 4 *Individual values for change in coronary sinus pH at the end of pacing (end) compared with the maximum change occurring in the 30 seconds after the end of pacing (peak). Zero refers to the coronary sinus pH at the start of pacing, and values are expressed as changes from this level, upwards indicating acidosis. Though mean pH in the ischaemic group at the end of pacing is significantly more acidic than in the non-ischaemic group ($p<0·005$) there is some overlap. The difference between the peak values, however, is highly significant ($p<0·001$) and only one value overlaps the dividing line of $-0·02$ units.*

the heart rate increases, however, distal vasodilatation becomes maximal, and then coronary flow through the stenosis becomes directly proportional to the diastolic pressure/time index, which falls with increasing heart rate. There is also some evidence that coronary vasoconstriction may occur as a result of thromboxane release.[17] Thus, absolute reductions in coronary flow distal to a stenosis may occur[5 6] affecting principally the subendocardium.[18]

Such a reduction in coronary flow in the presence of increased metabolic and oxygen demands results in ischaemia. Tissue accumulation of the end products of anaerobic metabolism such as lactate and hydrogen ion may be expected as a result of increased production and decreased washout. Even such a freely diffusible gas as carbon dioxide is found to be retained in the myocardium during pacing-induced ischaemia.[19] Although there is undoubtedly efflux of some small proportion of metabolites from the ischaemic area, the effluent is diluted by the increased venous effluent from non-ischaemic myocardium, so that the concentration of metabolites in venous blood changes relatively little during the period of ischaemia.

At the end of pacing, coronary flow to the non-ischaemic myocardium falls to control within six seconds[7] while the flow to the ischaemic area increases back to normal within three to five minutes.[6] The ischaemic area is "reperfused" and its retained metabolites washed out at a time when the dilution from non-ischaemic venous effluent is lessening.

It is not possible to estimate from our data whether the "washout" from the ischaemic area or the reduction in dilution by non-ischaemic effluent is more significant in causing the fall in coronary sinus pH after the end of pacing. A significant fall in coronary sinus pH did of course occur during pacing, indicating that there must have been efflux of hydrogen ions from the ischaemic area. This efflux was demonstrable despite the development of a mild arterial alkalosis which would result in an underestimation of coronary sinus acidosis. The results in the non-ischaemic group indicate the absence of excess acid efflux from non-ischaemic myocardium during the pacing test.

Our results with a continuous recording technique provide evidence of a fall in coronary sinus pH during ischaemia which becomes maximal in the 30 seconds after switchoff. Coronary sinus pH recording is technically difficult, and the construction of the electrodes time consuming, so that we do not at present foresee its widespread use. It seems likely, however, that the efflux of lactate into the coronary sinus will have a similar pattern to that of the hydrogen ion.[18] The sensitivity and specificity of coronary sinus lactate measurement during pacing in providing biochemical evidence of myocardial ischaemia in man may be considerably enhanced by sampling frequently during the first 30 seconds after the end of pacing.

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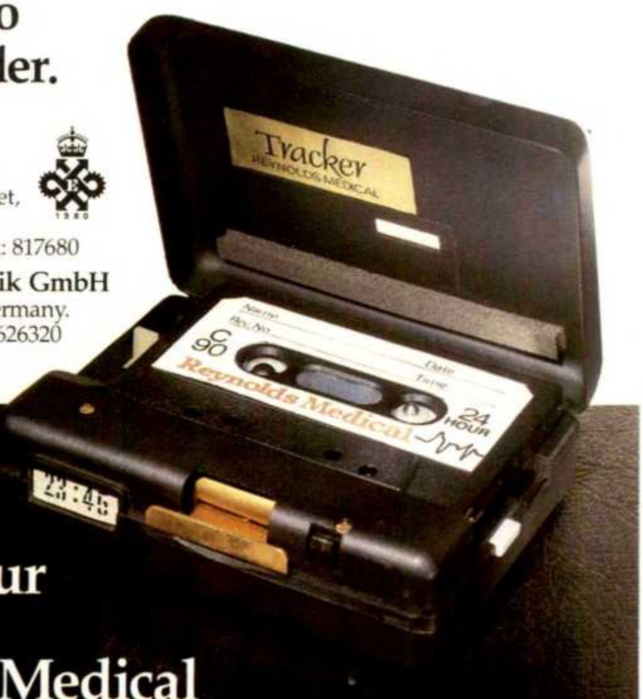

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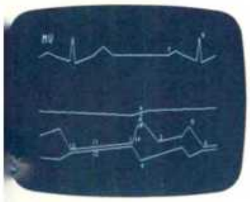

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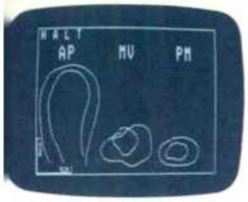

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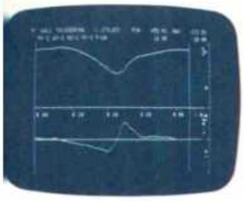

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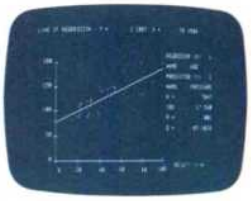

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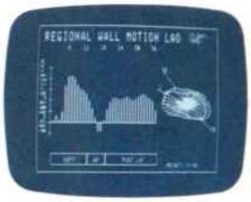

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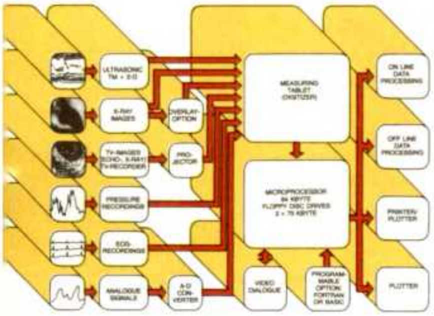

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Cardiovascular effects of prenalterol on rest and exercise haemodynamics in patients with chronic congestive cardiac failure

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SUMMARY The cardiovascular effects of the cardioselective $beta_1$ agonist prenalterol have been studied in nine patients with severe chronic congestive cardiac failure and in six patients with left ventricular dysfunction resulting from previous myocardial infarction. In the patients with cardiac failure intravenous prenalterol in a dosage of 1·5 μg/kg bodyweight increased the cardiac index from 1·8±0·1 to 2·1±0·1 l/min per m^2 and the left ventricular ejection fraction from 22±3 to 28±3%. There was a modest but significant increase in heart rate from 76±3 to 87±4 beats/min. Systemic vascular resistance fell from 2285±51 to 2041±534 dynes s^{-1} cm^{-5}. On exercise, the left ventricular filling pressure fell from 33±6 to 26±3 and both cardiac index and stroke index increased by 13% and 16%, respectively. There was no significant change in heart rate or systemic blood pressure. In the patients with left ventricular dysfunction, coronary sinus blood flow increased from 107±11 to 133±12 ml/min but the increase in myocardial oxygen consumption was small and not significant (11·6±1·2 and 14·5±1·9 ml/min). In all patients there was no evidence that prenalterol was arrhythmogenic.

There has been a resurgence of interest in the management of the patient with congestive cardiac failure. Vasodilator therapy has been shown to be effective in increasing cardiac output and reducing left ventricular filling pressure in patients with both acute and chronic cardiac failure[1-5]. Inotropic drugs can also be of value in improving cardiac performance but side-effects can be troublesome. Isoprenaline is a potent beta-adrenoreceptor agonist but provokes tachycardia, can precipitate arrhythmias, and increases myocardial oxygen consumption.[6] Dobutamine has been shown to have significant inotropic properties[7 8] but in patients after open-heart surgery a chronotropic effect similar to that of isoprenaline was found.[9] The endogenous catecholamine dopamine has been shown to be a useful inotropic agent and in addition dilates renal control and splanchic vessels. As with isoprenaline, however, it may provoke ventricular arrhythmias, and in addition it has alpha-adrenergic effects.[10] A combination of vasodilator therapy and inotropic agents has also been shown to be of value.[11 12]

Prenalterol (S-(-)-1-(4-hydroxyphenoxy)-3 isopropylamino propanol-2 hydrochloride) is a new selective $beta_1$-adrenoreceptor agonist which has been described as having potent inotropic effects with little chronotropic action.[13] Johnsson *et al.*[14] have reported that, in human volunteers, prenalterol when administered either orally or intravenously produced an increase in myocardial contractility with little or no increase in heart rate. Ariniego *et al.*[15] have confirmed these findings in patients with acute myocardial infarction and in addition suggested that prenalterol was a useful antidote to the unwanted cardiac effects of beta-adrenoreceptor blocking drugs. Hutton *et al.*[16] studied the haemodynamic effects in patients with coronary heart disease using both invasive and non-invasive methods and concluded that prenalterol enhanced the contractile state of the myocardium without altering heart rate. Reiz and Friedman[17] have reported that prenalterol is of value in improving the haemodynamic status of hypotensive patients with Gram-negative septic shock. Prenalterol appears to be effective both orally and parenterally and could well be of value in the management of the patient with acute and chronic cardiac failure.

The object of this study was to determine the effects of intravenously administered prenalterol on

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coronary haemodynamics in patients with left ventricular dysfunction and the effects on rest and exercise haemodynamics in a further group of patients with low output cardiac failure.

Patients and methods

CARDIAC FAILURE PATIENTS

Nine male patients, mean age 51±3 years (range 45 to 65 years), with severe chronic cardiac failure were studied. All patients were in sinus rhythm and were classified as functional class III (New York Heart Association). Six patients had coronary heart disease and three had idiopathic congestive cardiomyopathy. The clinical diagnosis of left ventricular dysfunction was confirmed by cardiac catheterisation and selective coronary angiography in all patients. Cardiac glycosides were withdrawn for seven days before the study and vasodilator therapy was withdrawn 48 hours before the study, but the patients' regular diuretic therapy was continued. Approval for this study was obtained from the Ethical Committee of the Glasgow Royal Infirmary and informed consent was obtained from each patient.

A Swan-Ganz catheter was inserted percutaneously into a peripheral vein for measurement of cardiac output, pulmonary pressure, and pulmonary capillary wedge pressure. Cardiac output was measured using the thermodilution technique (Instrumentation Laboratories 701). All cardiac outputs were measured in triplicate and the mean of the results was taken. Pressures were recorded using an Elcomatic transducer and recorded on a Mingograph 81 recorder. Blood pressure was obtained by sphygmomanometry. Heart rate was recorded continuously by means of a telemetered electrogram using a modified V5 chest lead electrode. Measurements were made at rest and during dynamic exercise. Upright exercise was performed on a mechanically braked bicycle ergometer at an individually predetermined "load" which was near maximal, usually within the range 25 to 50 watts, and which could be continued for three minutes.

Radionuclide angiography was performed after in vivo labelling of red blood cells with 20 mCi of technetium 99m pyrolite. After reaching equilibrium, electrocardiographically gated blood pool scintigrams were obtained in the left anterior oblique projection which provided optimal septal separation of right and left ventricular activity, using an Ohio Nuclear Series 100 Gamma Camera, interfaced to a Varian 620L computer. Left atrial activity was excluded using a 10° caudal tilt. Image data were stored in list mode with simultaneous acquisition of electrocardiogram and time. The computer was used to reconstruct 16 frames per cardiac cycle and the end-diastolic frame displayed. After background correction the left ventricular edge was identified for each frame using a thresholding technique validated in our laboratory.

Control haemodynamic data were obtained at rest and during exercise. Radionuclide angiography for technical reasons could only be performed at rest. Prenalterol was then infused intravenously over a 30 minute period using a calibrated infusion pump, in a dosage of 1·5 μg/kg bodyweight, and the above measurements repeated both at rest and during exercise. Continuous electrocardiographic monitoring was maintained after the completion of the study for a period of 12 hours while the patients were observed in a coronary care unit.

CARDIAC ISCHAEMIC PATIENTS WITH LEFT VENTRICULAR DYSFUNCTION

Six male patients with a mean age of 47±4 (37 to 59 years), who had sustained a previous myocardial infarction and had angiographic evidence of regional wall abnormality, were studied at the time of cardiac catheterisation. All drug treatment was discontinued over the 48 hours before the study.

Systemic blood pressure was obtained from an intra-arterial catheter placed in the ascending aorta via the femoral artery. Pulmonary pressure, pulmonary capillary wedge pressure, and cardiac output were measured as described above. A 7F double thermistor catheter (Wilton-Webster) was introduced into a left median antecubital vein and advanced into the proximal 1 to 2 cm of the coronary sinus. The catheter tip was not moved during the course of the study. Coronary sinus blood flow was measured using a continuous infusion thermodilution technique via a constant infusion of a 0·9% saline solution at 60 ml/min for 30 seconds.[18] The reproducibility of coronary sinus blood flow measurements using this technique is 3±2% and in this study relative effects were assessed with each patient acting as his own control. Simultaneous blood samples were obtained from the aorta and the coronary sinus and were assayed for oxygen content using an Instrumentation Laboratories Co-Oximeter 282.

Prenalterol was infused intravenously in a dosage of 1·5 mg in 50 ml of dextrose over a 30 minute period using a calibrated infusion pump.

Statistical analysis in both studies was performed using Student's paired t test, a p value of <0·05 being considered significant. The results are expressed as the mean ± standard error of the mean.

Results

CALCULATED VARIABLES

Systemic vascular resistance (SVR)=

$$\frac{(\text{MBP}-\text{RA})\times 80 \text{ dynes s}^{-1}\text{ cm}^{-5}}{\text{CO}}$$

Table 1 *Haemodynamic effects of prenalterol in patients with chronic cardiac failure*

	Rest		*Exercise*	
	Control	*Prenalterol*	*Control*	*Prenalterol*
Heart rate (beats/min)	76±3	87±4‡	125±10	120±7
Systolic blood pressure (mmHg)	120±6	130±7†	157±12	163±13
Diastolic blood pressure (mmHg)	75±3	75±4	—	—
Mean blood pressure (mmHg)	90±4	94±4	—	—
Cardiac index (l/min per m^2)	1·8±0·1	2·1±0·1†	3·0±0·3	3·4±0·2
Stroke index (ml/m^2)	24±2	24±2	25±2	29±3
Pulmonary capillary wedge (mmHg)	19±2	17±2	3±6	26±3*
Ejection fraction (%)	22±3	28±3†	—	—
Stroke work index (g m/m^2)	23±4	25±3	25±4	31±5
Systemic vascular resistance (dynes s^{-1} cm^{-5})	2285±193	2041±201*	1733±134	1414±187*

Results are mean ± SEM of nine patients $^*p<0{\cdot}05$ $^\dagger p<0{\cdot}02$ $^\ddagger p<0{\cdot}005$.

where MBP is mean blood pressure (mmHg), RA is mean right atrial pressure (mmHg), CO is cardiac output (1/min).

Stroke work index $(SWI)=(MBP-LVEDP)\times SI\times 0{\cdot}0136$ g/m per m^2

where LVEDP is left ventricular end-diastolic pressure (mmHg) and SI is stroke index (ml/m^2).

CARDIAC FAILURE GROUP

The detailed haemodynamic results are shown in Table 1.

At rest, prenalterol produced significant increases in cardiac index from 1·8±0·1 to 2·1±0·1 l/min per m^2 ($p<0{\cdot}02$) and in left ventricular ejection fraction from 22±3 to 28±3% ($p<0{\cdot}02$) (Fig. 1). There was a modest but significant increase in heart rate from 76±3 to 87±4 beats/min ($p<0{\cdot}005$) and in systolic blood pressure from 120±6 to 130±7 mmHg ($p<0{\cdot}02$) (Fig. 2). Systemic vascular resistance fell from 2285±511 to 2041±534 dynes s^{-1} cm^{-5} ($p<0{\cdot}05$).

On exercise, left ventricular filling pressure fell from 33±6 to 26±3 mmHg ($p<0{\cdot}05$) and both cardiac index and stroke volume increased by 13% and 16%, respectively. Systemic vascular resistance fell from 1733±134 to 1414±184 dynes s^{-1} cm^{-5} ($p<0{\cdot}05$). There was no significant change in heart rate or systemic blood pressure (Fig. 3). All patients tolerated the drug well and did not complain of palpitation or angina pectoris. No evidence of significant ventricular extrasystoles was found on the continuous recording electrocardiogram.

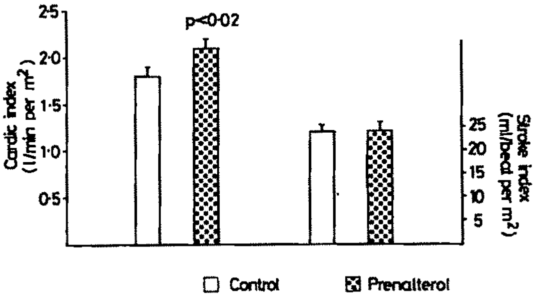

Fig. 1 *The effects on cardiac index and stroke index at rest, after the intravenous administration of prenalterol in a dosage of 1·5 μg/kg bodyweight.*

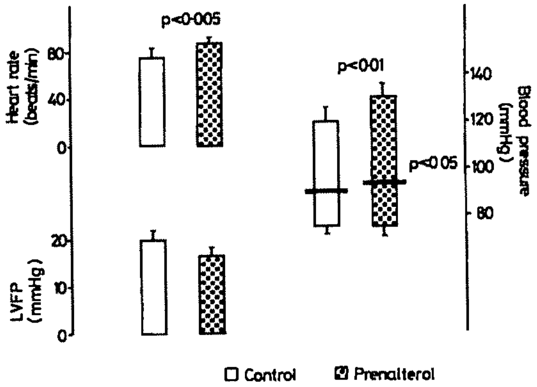

Fig. 2 *The effects on heart rate, left ventricular filling pressure, and blood pressure after intravenous administration of prenalterol. The bars indicate mean blood pressure, at rest.*

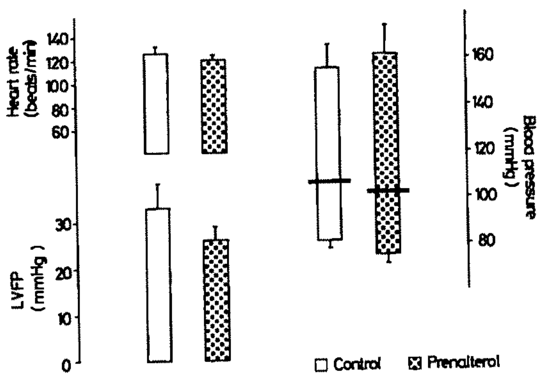

Fig. 3 *The effects on heart rate, left ventricular filling pressure, and blood pressure during dynamic exercise, after intravenous administration of prenalterol. The bars indicate mean blood pressure.*

CARDIAC ISCHAEMIC PATIENTS WITH LEFT VENTRICULAR DYSFUNCTION

The detailed haemodynamic findings are shown in Table 2. In these patients with left ventricular regional wall abnormalities, prenalterol increased cardiac index from 3·1±0·2 to 3·6±0·3 l/min per m^2 ($p<0\cdot02$). There was a modest but significant increase in heart rate from 74±4 to 90±6 beats/min ($p<0\cdot005$). There were no significant changes in systemic blood pressure or in left ventricular filling pressure. Coronary sinus blood flow increased from 107±11 to 133±12 ml/min ($p<0\cdot05$) but with an associated but not significant increase in myocardial oxygen consumption from 11·6±1·2 to 14·5±1·9 ml/min (Fig. 4).

Table 2 *Haemodynamic effects of prenalterol in patients with left ventricular dysfunction*

	Control	*Prenalterol*
Heart rate (beats/min)	74±4	90±6‡
Systolic blood pressure (mmHg)	115±7	116±2
Diastolic blood pressure (mmHg)	71±4	73±2
Mean blood pressure (mmHg)	87±6	88±3
Cardiac index (l/min per m^2)	3·1±0·2	3·6±0·3†
Stroke index (ml/m^2)	42±4	41±4
Pulmonary capillary wedge (mmHg)	9±1	7±1
Coronary sinus blood flow (ml/min)	107±4	133±12*
Myocardial oxygen consumption (ml/min)	11·6±1·2	14·5±2

Results are mean ±SEM of six patients.
*$p<0\cdot05$ †$p<0\cdot02$ ‡$p<0\cdot005$.

Discussion

This study has shown that prenalterol enhances the cardiac performance of patients with congestive cardiac failure both at rest and during dynamic exercise as reflected by significant increases in cardiac output and left ventricular ejection fraction. The reduction in left ventricular filling pressure appears to be secondary to a positive inotropic action, but there was a modest but significant fall in systemic vascular resistance suggesting that a degree of peripheral vasodilatation might be contributing to the improvement in ventricular performance. The increase in systolic blood pressure with a decrease in systemic vascular resistance again suggests that the principal action of prenalterol is to increase myocardial contractility. In addition there was a slight but significant increase in heart rate at rest, indicating a chronotropic response mediated through the beta$_1$ cardiac receptors.

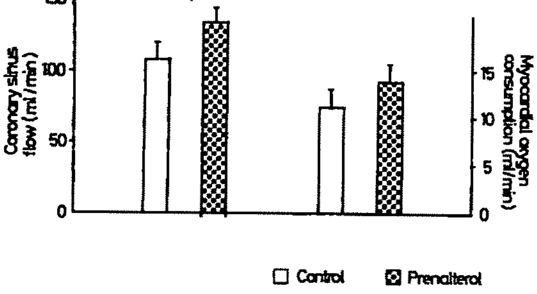

Fig. 4 *The effects on coronary sinus flow and myocardial oxygen consumption at rest, after the intravenous administration of prenalterol.*

In the presence of coronary artery obstruction, inotropic agents which increase myocardial oxygen consumption have to be used with caution.[19] None of the patients with cardiac failure experienced angina pectoris, and in the patients with left ventricular dysfunction, who all had a history of angina pectoris, prenalterol did not provoke cardiac pain. In the latter group, though there was an increase in myocardial oxygen consumption, there appeared to be a greater increase in coronary blood flow. In our previous study with patients who had recently sustained an acute myocardial infarction the administration of prenalterol did not provoke angina pectoris.[16] This has been confirmed by Ariniego *et al.*[15] with prenalterol and by Gillespie *et al.*[20] with dobutamine in patients with acute myocardial infarction.

No evidence of ventricular arrhythmias nor indeed of increased ventricular extrasystoles was found in this study but Kirlin and Pitt[21] have reported that ventricular tachycardia occurred in two out of nine patients with severe low output cardiac failure after the intravenous administration of prenalterol. It should be noted that these patients were having frequent ventricular extrasystoles before the start of the study and all were receiving concomitant digitalis therapy which suggests that the combination of prenalterol and digoxin may induce ventricular arrhythmias.

The only oral inotropic agents used in clinical practice are the cardiac glycosides which have a narrow toxic therapeutic ratio, and hence toxicity, including ventricular arrhythmias, is not uncommon and has been reported in as high a percentage as 20% of a hospital population.[22]

There is considerable controversy about the efficacy of digitalis as an inotropic agent in the patient with cardiac failure who is in sinus rhythm. Goldstein *et al.*,[23] in patients with acute myocardial infarction and cardiac failure, found little improvement after intravenous digoxin, as did Hodges *et al.*[24] Arnold *et al.*[25] and Murray *et al.*[26] have reported that both intravenous and chronic oral digoxin therapy have a modest but definite positive inotropic effect in patients with chronic congestive cardiac failure, particularly during dynamic exercise. There thus appears to be a place for new oral inotropic agents in the management of patients with chronic congestive cardiac failure.

Prenalterol has been shown to be effective orally in both normal volunteers and patients with congestive cardiac failure where an increase in cardiac output and reduction in left ventricular filling pressure were found with an improvement in functional exercise capacity.[27] It therefore seems appropriate to evaluate the haemodynamic effects of oral prenalterol in chronic congestive cardiac failure over a prolonged period, though Braunwald has raised the possibility that prolonged administration of a beta-adrenergic agonist might lead to alteration of haemodynamic responses, a consequence of "down-regulation" of the beta receptor.[28]

This study has shown that intravenous prenalterol improves cardiac performance in patients with chronic congestive cardiac failure, and a placebo-controlled trial of oral prenalterol in such patients appears indicated.

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Br Heart J 1982; 47: 381–91

Evaluation of mild acute infectious myocarditis

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SUMMARY The diagnosis of acute mild myocarditis is vaguely defined. Therefore we studied 185 consecutive young men in military service with electrocardiographic changes arousing a suspicion of myocarditis in connection with an acute infectious disease. It was possible to classify 160 patients into seven electrocardiographic groups; definite or probable myocarditis was observed in 104 patients. The electrocardiographic patterns considered characteristic for acute myocarditis were: ST segment elevations followed by T wave inversions; gradually changing T wave inversions not corrected by beta blockade; and ventricular extrasystoles more than 10 per minute triggered by acute infection. Thirty-nine subjects without myocarditis had "functional" T wave abnormalities completely normalised by beta blockade, or stable T wave inversions.

The leading symptoms in acute myocarditis were fatigue and chest pains; loud S_3 gallop, paradoxical cardiac pulsation, pericardial friction rub, or enlargement of the heart were noted altogether in 50% of the patients. Echocardiography disclosed segmental wall motion abnormalities related to the T wave inversions. Serum creatine kinase MB fraction increased in 70% of the acute myopericarditis patients during the ST segment elevation stage. In the non-myocarditis groups the clinical and pertinent laboratory findings remained normal.

Thus, we noted in clinically mild acute infectious myocarditis clear-cut and early signs of myocardial dysfunction, suggesting that the direct and often local viral invasion of the myocardium is the basic pathogenetic mechanism. The present electrocardiographic classification based on serial tracings and beta blockade proved useful in the evaluation of patients suspected of having mild acute myocarditis.

Severe acute myocarditis does not usually give rise to diagnostic difficulties, since gross cardiac enlargement and often progressive heart failure are clinically self-evident. Such a course of infectious myocarditis is rare.[1] In contrast, mild often clinically asymptomatic myocarditis is common.[2] Diagnosing even mild acute myocarditis is necessary, as these patients may be in danger of sudden cardiac death,[3] or may insidiously develop congestive cardiomyopathy.[4]

Diagnosing subclinical viral myocarditis depends essentially on an electrocardiogram at the initial stage of the disease.[2 5] It is, however, also obvious that functional electrocardiographic abnormalities noted in connection with acute infectious disease and fever, and changes caused by other cardiac disease should not necessarily indicate acute myocardial involvement.[6 7]

This report reviews our experience with the clinical evaluation of patients with various electrocardiographic abnormalities arousing a suspicion of acute myocarditis in conjunction with, for example, an acute respiratory or gastroenteric infection. We particularly intend to propose an electrocardiographic classification, which we have found useful in the evaluation of patients in whom mild acute myocarditis may be present.

Methods

PATIENTS

One hundred and eighty-five patients were thoroughly examined at Central Military Hospital 1 in Helsinki. The patients were either conscripts in compulsory military service or young military personnel 18 to 38 years old, median age 20 years. They had been admitted because of electrocardiographic abnormalities which were noted in the course of an acute infectious

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disease. This consecutive series was collected during the period December 1976 to December 1980. There were two different ways of including patients in the study series: (1) Patients whose electrocardiograms were recorded because of clinical symptoms or signs possibly related to acute myocarditis or pericarditis (63% of the study population); (2) patients taken for a prospective study (37% of the study population) initiated in January 1978 to examine the incidence and clinical picture of acute mild myocarditis in connection with respiratory or gastrointestinal infection, irrespective of any cardiac symptoms. In three garrisons, a 12 lead electrocardiogram was recorded from all conscripts with acute infective symptoms, as partially reported previously.[5] In the prospective series an electrocardiogram was recorded on the first and third days of the disease, and two weeks later.

Each patient was clinically examined within two weeks of the initial electrocardiographic changes. The follow-up time was two to 12 months after the acute stage and always lasted until the electrocardiogram reverted to normal, or up to 12 months after the acute stage in the case of permanent electrocardiographic abnormalities.

CLINICAL SYMPTOMS AND SIGNS

Chest pain was recorded as being extracardiac, pericardial, or mimicked coronary pain. The patients were asked about other subjective symptoms, such as palpitations.

A physical examination was made by both authors; particular attention was paid to palpation of the cardiac thrust and to auscultation. The cardiac palpation was classified as follows: normal apical beat only, uncertain asynergic contraction, or distinct paradoxical precordial motion. The S_3 gallop was classified as none, weak and disappearing in the sitting position, or loud, also in the sitting position. This positional analysis was thought to help in separating the normal ventricular rapid filling sound present in young subjects with hyperkinetic circulation (physiological S_3) from sounds in those with myocardial involvement.

LABORATORY EXAMINATIONS

Serial 12 lead electrocardiograms were usually recorded daily during the first week of the acute illness and thereafter at one to two week intervals until the ST-T changes reverted to normal. The method of classification for the electrocardiograms is presented in the results. *The beta blockade test* was performed to differentiate the T wave inversions caused by acute myocarditis or some other organic cause from "functional" T wave inversions.[7] An electrocardiogram was recorded supine at rest and after standing for three minutes, and was repeated two hours after the oral administration of the beta-blocking drug, usually 100 mg metoprolol. The test was considered adequate if the heart rate at rest decreased by 10% or more. Chest x-rays and serial echocardiograms[8] were taken in all patients.

Positive serological findings indicating a viral or other specific infectious cause of the acute illness were found in 47% of the myocarditis patients. These will be published separately; aetiology was viral in 80% of the patients, the three most common agents being adeno, influenza, and vaccinia virus.

The patients' serum creatine kinase (normal level <220 IU/l), aspartate aminotransferase, and alanine aminotransferase (normal levels <40 U/l for both) were determined: in 65 of 160 patients this was possible during the first week of the infectious disease. The creatine kinase isoenzymes were assessed electrophoretically and quantified by fluorometric scanning, using the method of Somer and Konttinen[9]; 0·03 of total creatine kinase was taken as upper limit of normal.

Results

ELECTROCARDIOGRAPHIC CLASSIFICATION OF STUDY POPULATION

Of the 185 consecutive patients 160 could be classified into the following seven groups, based on serial resting electrocardiograms and on the response of the ST-T waves to beta adrenergic blocking drugs. Diagnosis of definite or probable acute myocarditis, or no myocarditis, was based on serial electrocardiographic data only, as described below.

Definite myocarditis (groups 1 and 2)

Myopericarditis: group 1: the serially changing electrocardiographic ST segment and T wave alterations were characteristic of the well-established abnormalities of "acute pericarditis".[10] The initial ST segment elevation of 0·1 mV or more in several leads is gradually replaced in this group by an inversion of the T waves (Fig. 1).

The ST segment elevations were noted in 34 patients and were widely distributed in 56% of the patients. The subsequent T wave inversions taking place in these patients, however, were usually only local, 88% (Table 1). The gradual changes in the ST segment elevations and T wave inversions generally had a duration of six to eight weeks, the initial ST segment elevation returning to normal in one week.

The beta blockade test was performed in 15 patients at the T wave inversion stage. No patient showed less T wave inversion after beta blockade; it often became more prominent (Fig. 2). During late convalescence, however, functional-type, vacillating T wave variations were also commonly noted before

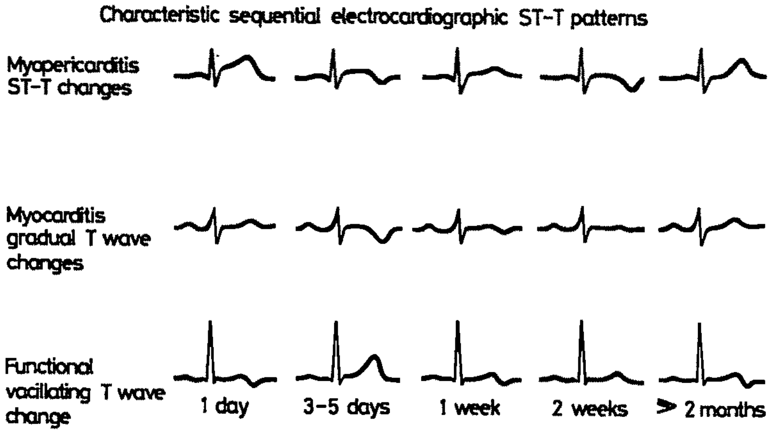
Characteristic sequential electrocardiographic ST-T patterns
Myopericarditis ST-T changes
Myocarditis gradual T wave changes
Functional vacillating T wave change
1 day
3-5 days
1 week
2 weeks
> 2 months

Fig. 1 *Schematic representation of serial ST-T patterns of myopericarditis, myocarditis, and non-myocarditis states.*

Table 1 *Site and duration of ST-T changes in 34 patients with myopericarditis (group 1) and 22 patients with myocarditis (group 2)*

Site			*Duration*		
Electrocardiographic lead	*No. of cases*		*Mean days*	*No. of cases*	
	ST↑	*T*↓		*>1 month*	*<1 month*
General: I, II, III, aVL, aVF, V3-6					
Myopericarditis ST-T changes	19	4	34	3	1
Myocarditis T wave changes		1	5		1
Inferoapical: II, III, aVF, V3-6					
Myopericarditis ST-T changes	9	19	47	15	4
Myocarditis T wave changes		15	17	3	12
Anterolateral: I, II, aVL, V3-6					
Myopericarditis ST-T changes	6	11	45	9	2
Myocarditis T wave changes*		5	53	3	2

*One patient had anteroseptal T wave inversions in V2-4.

the permanent return to normal of the electrocardiogram.

Myocarditis T wave inversion: group 2: the 22 patients included in this group had a pattern of gradually changing T waves in at least two leads, excluding leads aVR and V1 where the T wave may be normally negative. First there was a gradual inversion of the T waves and subsequently their gradual return to normal. The T wave inversions had to last four days or more. An equivalent change was considered to have taken place if the T waves were already initially maximally inverted but thereafter showed a pattern of gradual return to normal. In this group it was also necessary that these gradual T wave inversions did not improve after an effective dose of beta-blocking drug, as described in the methods.

T wave inversions were located in the inferoapical region in the majority of patients (68%), while anterolaterally located changes showed the longest duration (Table 1). The most characteristic sequence of the electrocardiographic abnormalities was an almost simultaneous inversion of the T waves in leads II, III, aVF, and V4-6 to maximum negativity as early as days one to three of the infection. Thereafter the gradual return to normal always followed the same sequence: the chest leads first reverted to normal, followed by leads II and aVF, and finally lead III (Fig. 2).

Probable myocarditis (groups 3 and 4)

Probable myocarditis T wave inversion: group 3: 34 patients showed a pattern of gradual T wave changes similar to that described in group 2; in fact the only difference was that no confirming beta blockade test was available for this group.

Ventricular extrasystoles of recent onset: group 4: ventricular extrasystoles were first noted during, or soon after, an acute infection as a presenting symptom in

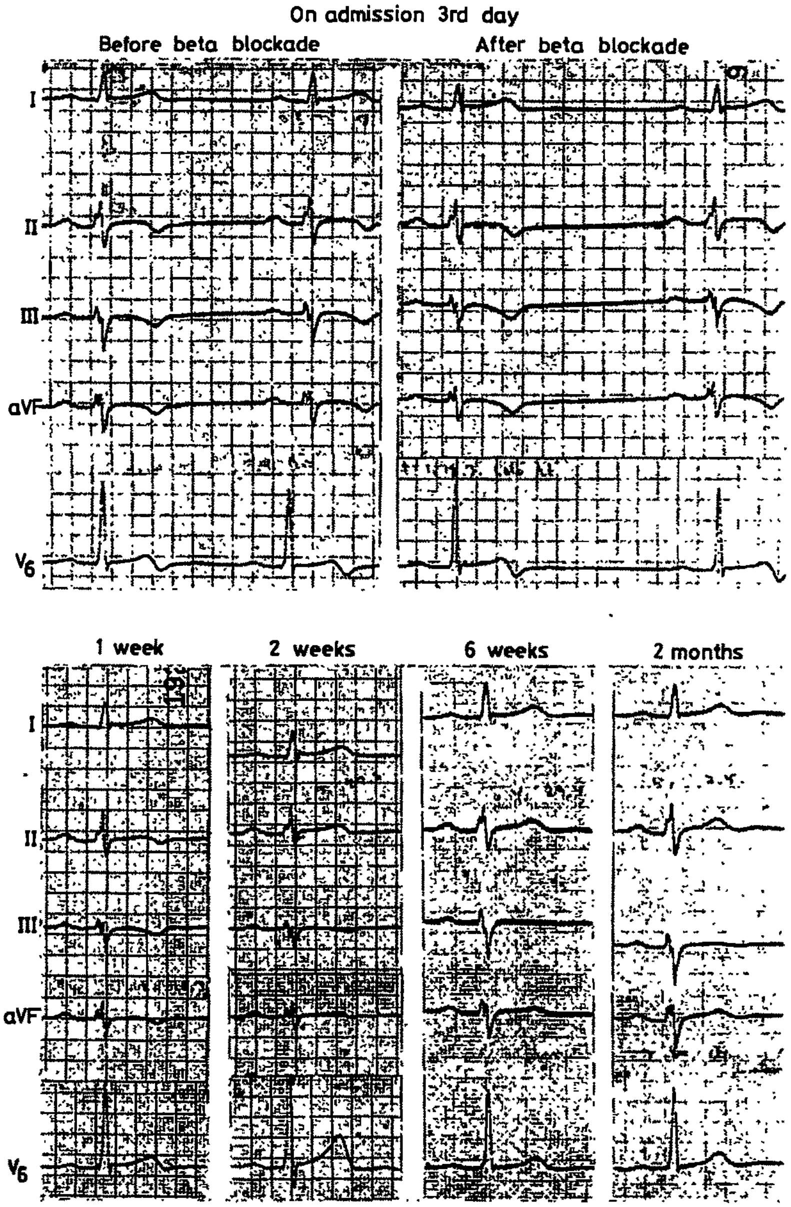

Fig. 2 *Characteristic sequence of the gradually changing inferoapical T wave inversion.*

this group, and the serial electrocardiograms showed no pronounced ST-T changes. Extrasystoles had an occasional frequency of at least 10 beats per minute. Further, the patient himself had to feel that this cardiac irregularity was a new symptom.

The ventricular extrasystoles were, with only one exception, unifocal and septal in origin. In four of the 14 patients included in this group, the mechanism was unequivocally parasystolic; two patients experienced ventricular tachycardia. In 11 of the 14 patients (79%) the ventricular extrasystoles either increased in frequency (nine patients) or else were not changed by the bicycle exercise test. The arrhythmias lasted less than two months in three patients; the others had extrasystoles throughout the follow-up periods of three to 10 months. Five patients also had gradually changing minor T wave inversions for up to two weeks at the initial stage of the disease.

Short-term myocarditis-type T wave inversions: group 5

The 17 patients included in this electrocardiographic group had a gradual T wave inversion pattern during an acute infection. These T wave inversions, however, were present for only one to three days and no beta blockade test was available. No "functional", "vacillating" T wave behaviour was noted. All but one of the T wave inversions were local: eight inferoapical and eight local anterior in leads V2, V3, and/or V4.

Patients without myocarditis (group 6 and 7)

"Functional" T wave changes: group 6: the alterations in the T waves did not show the gradually changing pattern in the serial electrocardiograms described above, but instead vacillated irregularly between a normal and an abnormal shape. This group included 25 patients initially suspected of having acute myocarditis. The T wave abnormality was augmented without exception during the standing position and often during sinus tachycardia in supine rest. Even when the resting tracing was normal, the "vasoregulatory" T wave inversions were always generated orthostatically. These "vacillating", "functional", or "vasoregulatory" T wave inversions returned completely to normal as a result of beta blockade. T wave inversions of this type were never seen in leads I and aVL. The functional T wave inversions were present only during fever in some patients, while in others this fluctuation was permanent.

Stable T wave inversions: group 7: permanently negative T waves, without clinical signs of acute myocarditis, were noted in 14 patients. Such T waves did not show any gradually changing patterns though minor variations in the amplitudes of the negative T waves were possible. Beta blockade either enhanced the T negativity or else did not have any influence on it. Some of these patients had aortic valve disease or cardiomyopathy; in most, no definite organic cardiac pathology was found.

Exclusions

Of the 185 subjects included in the present study population in connection with an acute infection, 25 were excluded from the seven electrocardiographic groups defined above. Three patients may have had mild myocarditis, one of them developed a new right bundle-branch block and prolongation of the PQ interval, while two had ST depressions only during the bicycle exercise test. The other findings were: early repolarisation-type ST segment elevation (10 subjects), supraventricular arrhythmias (four), functional T wave changes, not included in group 6 because the beta-blockade test remained insufficient (three), sport heart (two), ventricular extrasystoles of long duration (one), mitral valve prolapse (one), and hypertrophic obstructive cardiomyopathy (one).

Data provided by prospective electrocardiographic screening

Only a few patients with the myopericarditis type of electrocardiogram (group 1) or with ventricular extrasystoles of recent onset (group 4) were identified in the prospective screening (Table 2). The majority of the subjects with "functional" T wave changes (group 6) were naturally detected by this screening method.

It is worth noting that all the patients who had electrocardiographic findings, which mainly pointed to definite or probable myocarditis, already showed these changes in tracings taken on the first and/or third day of the onset of the infectious disease.

CLINICAL FEATURES RELATED TO ELECTROCARDIOGRAPHIC CLASSIFICATION

The occurrence of the symptoms and physical findings in the different patient groups is summarised in Table 3. Clinically clear-cut myopericarditis was usually caused by vaccinia, mononucleosis, mycoplasma, chlamydia, and Coxsackie B4 infections. Adenovirus and influenza myocarditis were most often only detected by serial electrocardiographic screening.

Table 2 *Distribution of patients with various electrocardiographic presentations; 59 of 160 patients (37%) emerged from prospective screening of patients with infection*

Group	*1*	*2*	*3*	*4*	*5*	*6*	*7*
ECG definition	*Myopericarditis*	*Myocarditis-type T wave inversions*		*Extrasystoles related to infection*	*Short-term T wave inversions*	*Functional T wave changes*	*Stable T wave inversions*
Diagnosis of myocarditis	Definite	Definite*	Probable†	Probable	Possible	No‡	No*
Total no. of patients	34	22	34	14	17	25	14
Prospective screening (%)	2 (6)	11 (50)	15 (44)	1 (8)	8 (47)	19 (76)	3 (21)

*Beta blockade did not normalise inverted T waves.
†Beta blockade test not performed.
‡Beta blockade normalised the inverted T waves.

Table 3 *Symptoms and signs in 160 patients of study series*

Group no.	*1*	*2*	*3*	*4*	*5*	*6*	*7*
Total no. of patients	*34*	*22*	*34*	*14*	*17*	*25*	*14*
Fatigue	15	7	12	11	4	6	4
Pain							
None	8	12	25	8	10	15	9
Extracardiac	5	5	3	2	4	8	4
Pericardial	14	4	4	2	1	1	1
Coronary mimicking	7	1	2	2	2	1	0
Palpation							
Normal	12	13	21	5	11	21	12
Borderline	11	3	7	6	5	4	1
Paradoxical	11	6	6	3	1	0	1
S3							
None	10	15	15	7	9	11	9
Physiological	7	3	10	4	5	13	3
Abnormal	17	4	9	3	3	1	1
S4							
Present	2	0	0	0	0	0	0
Pericardial rub							
Present	10	4	5	0	0	0	0
Heart size							
Enlarged	7	2	8	6	1	0	0

Exceptional fatigue continuing after the initial stage of the infection appeared to be more common (38%) in the patients with myocarditis (groups 1 to 3) than in groups 6 to 7 (26%) with no myocarditis. The patients with recent ventricular extrasystoles felt prolonged fatigue very often (79%). The pericardial type of chest pain and "coronary mimicking" pain were most common in the myopericarditis group (41% and 21%, respectively).

A pathological cardiac palpatory finding was noted in 25% of patients with definite or probable acute myocarditis; a borderline abnormal finding was noted in a further 26%. The paradoxical cardiac thrust did not have as high an amplitude as is found in acute myocardial infarction, but it was commonly pansystolic (Fig. 3). It was an initial physical finding; in only two patients did it appear two weeks after the first electrocardiographic findings. An S_3 gallop was a frequent auscultatory finding (52%). In the myocarditis groups the S_3 gallop was frequently loud and also persisted in the sitting position (30% of the 104 patients); it was rare (5%) in the 39 patients without myocarditis. A pericardial rub was heard only in patients with the ST and/or T wave changes classified as indicating myopericarditis or myocarditis. A rub was heard in 29% of the patients with ST segment elevations, and in 16% of the patients with gradual T wave changes. No patient in this series of infectious myocarditis developed congestive heart failure.

Altogether, one or several findings of a loud S_3 gallop, cardiac palpatory asynergy, or pericardial rub was present in 52 of the 104 patients in the myocarditis groups 1 to 4.

CHEST X-RAYS

The cardiac size was normal and did not show any enlargement in the hospital follow-up in the non-myocarditis patients (groups 6 and 7). The heart became enlarged in only one of the 17 patients in group 5 with short-term T wave changes. An abnormal heart size was seen in 22% of the 104 myocarditis patients (groups 1 to 4). Notably, this abnormality occurred most often in the ventricular arrhythmia group: in six of the 14 patients (43%). Conspicuous pulmonary venous congestion did not occur in these patients.

SERUM ENZYMES

Serum *aspartate aminotransferase* activity was increased during the first week only in the patients with myopericarditis ST segment changes (Fig. 4).

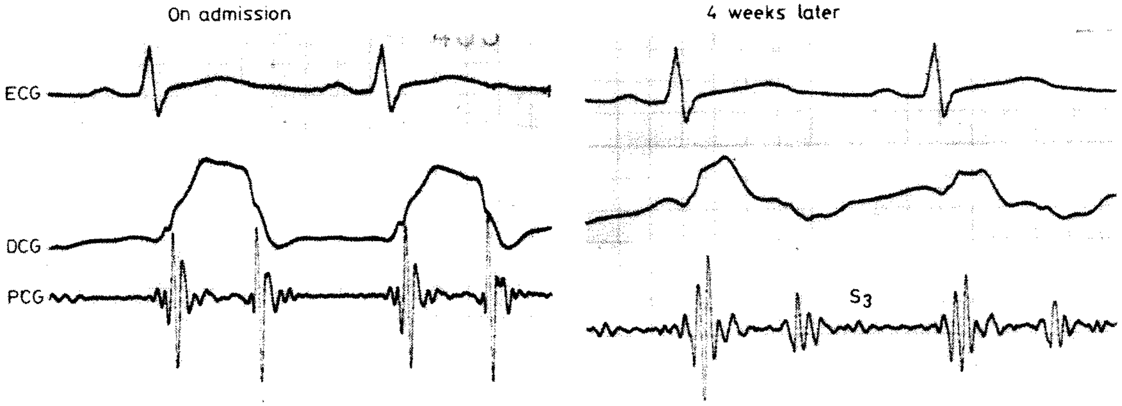

Fig. 3 *Kinetocardiogram in an acute stage of myocarditis, confirming the palpable paradoxical cardiac pulsation. This method of recording the precordial displacement curve gives absolute precordial motion, not relative motion as with the apexcardiogram. The normal curve is mainly negative. Four weeks later the asynergic motion is less. Note also the third sound.*

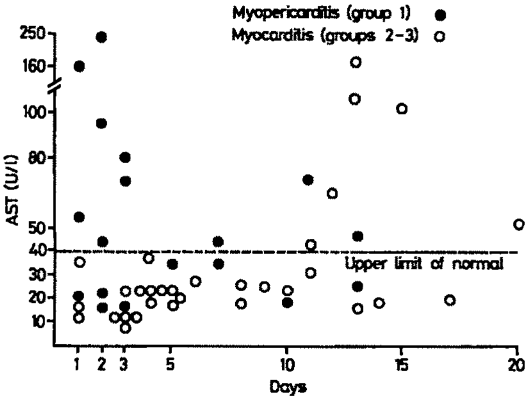

Fig. 4 *Serum aspartate aminotransferase (AST) elevations were noted only during the initial days in the patients with myopericarditis but not in those with myocarditis-type T wave changes only. After the first week, however, new increases were noted, probably reflecting hepatic involvement.*

The highest values were noted in those patients who also had the highest creatine kinase MB (CK MB) levels. Abnormal values lasting over the first week of the disease were noted in nine patients and only if *alanine aminotransferase* was increased at the same time; this late increase was observed also in some patients with T wave changes only.

CK MB

Fig. 5 shows the CK MB activities in 18 of the 34 myopericarditis patients (group 1). In only 10 patients, however, was the determination performed during the first six days, at the stage of ST segment elevation. Increases in CK MB occurred only during the first days of the disease; values exceeding the normal upper level 0·03 of the total creatine kinase were noted in seven patients. These seven patients all had chest pains, initial ST segment elevations, and thereafter deep T wave inversions lasting several weeks (Fig. 6). The highest level, 186 IU/l, was measured in a patient with repetitive bursts of ventricular tachycardia during the first two days of myopericarditis (see Fig. 8). No CK MB abnormalities occurred during the later T wave inversion stage.

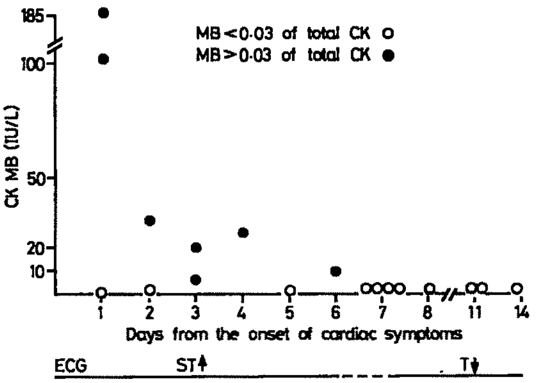

Fig. 5 *Serum creatine kinase MB fraction (CK MB) levels studied from 18 patients with myopericarditis (group 1) were abnormal only during the initial days, at the stage of ST segment elevations.*

In groups 2 and 3 (myocarditis-type T wave inversions only) CK MB determinations were available during the first six days of the disease in 28 patients. Only three patients had an activity greater than 0·03 fraction of the total CK level. All CK MB determinations made after the first week of the disease remained negative.

In groups 4 to 7 the CK MB activities were determined in 27 patients within six days: they always remained normal.

RECOVERY FROM MYOCARDITIS

Electrocardiographic abnormalities lasted more than 100 days in only three of the 56 patients in the definite myocarditis groups; 11 patients complained of easy fatigue, tiredness, sharp chest pains, and palpitation when they were re-evaluated six months later. Such symptoms were persistently present in four of 34 patients in group 3, and in four patients in the extrasystolic group. Altogether 16·8% had these symptoms. Notably, the new extrasystoles persisted at this time in 10 of the 14 patients.

Discussion

ELECTROCARDIOGRAPHIC PATTERNS IN MILD ACUTE MYOCARDITIS

The clinical diagnosis of myocarditis is often a problem.[11] This is reflected by such general statements as: "there are no established clinical criteria in the diagnosis of myocarditis", or "the clinical features of viral myocarditis are variable".

Electrocardiographic criteria for acute myocarditis are also vague and non-specific. Most of the difficulties are caused by various ST-T alterations appearing during fever and in subjects showing functional T wave inversions in vasoregulatory lability.[7 12 13] In this sense the relevance of the electrocardiographic classification suggested here is discussed below.

Myopericarditis group

The electrocardiographic pattern of "acute pericarditis" with serially changing ST segment elevations and subsequent T wave inversions is easiest to assess.[10] The essential role of the myocardial damage itself in causing the characteristic ST-T changes in these patients is pointed out by the ventricular gallop sound

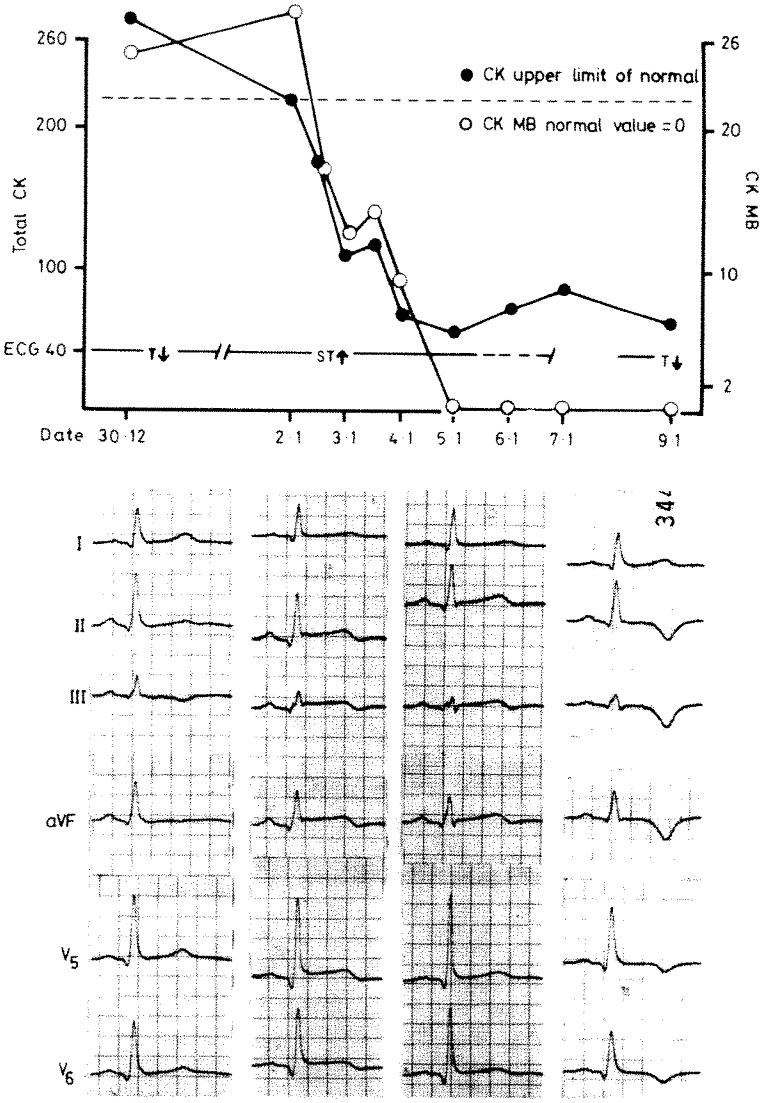

Fig. 6 *Serial electrocardiograms from patient with myopericarditis are related to serial total creatine kinase (CK) and MB fraction (CK MB) enzyme levels. On admission the patient had chest pains and negative T waves in inferior leads, followed in a couple of days by pericarditis-type ST segment elevations. Note the very early occurrence of the enzyme elevations, which returned to normal during the first week. CK MB remained abnormal during two days when total creatine kinase had already returned to normal.*

and palpable ventricular asynergy, observed in two-thirds of our patients in this group. Further, serum enzymes were raised during the first days of the disease, as in acute myocardial infarction. While the ST segment elevations were usually widespread, the subsequent T wave inversions were local, indicating the focal nature of the myocardial damage in mild myocarditis. This conclusion is supported both by our echocardiographic findings on regional left ventricular asynergy[8] and by recent radionuclide techniques indicating local myocardial damage in Coxsackie and echo virus myocardial disease.[14 15]

Myocarditis T wave inversions

The serial T wave inversions in patient groups 2 and 3 were classified as organic changes because of their appearance with acute infection, the gradually changing pattern of the repolarisation changes, and finally their unresponsiveness to beta blockade. Several clinical features indicate that this electrocardiographic manifestation usually reflects a milder degree of myocarditis than is the case in patients with "classic" ST-T patterns. Thus, while the pathological S_3 gallop and palpatory cardiac asynergy and pericardial rub were also noted frequently in these patients, they occurred less frequently than they did in group 1 (16 to 39%). Myocardial enzyme increases were rare in these patients. Furberg[7] found that the "organic" T wave inversions were not returned to normal by beta blockade. Our series confirms completely his early findings, that is no return to normal, often even worsening, of the T wave inversions.

Recent ventricular extrasystoles

The following features in the patients with new and electrocardiographically ventricular extrasystoles may indicate underlying acute myocarditis: new appearance in connection with an acute infectious disease, extraordinary fatigue during convalescence, a pathological S_3 gallop, and cardiac asynergy on palpation during normal heart beats (in 23% of this group). In most patients, the ventricular extrasystoles were increased by physical exercise. Cardiac enlargement was noted in the chest *x*-rays of 43% of these patients, while this change occurred in less than 20% in all the other groups.

Abnormalities in the upper septal ventricular region may cause only minor electrocardiographic changes,[16] so that the only evidence of involvement may be arrhythmia. The site of the extrasystoles was indeed most often septal, and our echocardiographic evaluation also usually indicated septal abnormalities, as will be reported separately.

Short-term myocarditis-type T wave inversions

This group is most difficult to assess: some patients may have minor myocarditis, while others probably have other reasons for the transient nonspecific repolarisation changes, such as functional T wave changes. Though some of the patients may have had minor myocardial involvement, it nevertheless gave an impression of being clinically insignificant.

Functional T wave changes

"Functional", "vasoregulatory", "vacillating" T wave inversions were characteristically always augmented in the standing position but beta blockade completely restored to normal the T wave inversion. Functional T wave changes are not uncommon among healthy persons but may inadvertently arouse a suspicion of myocarditis during an acute infection.[6 13 17] Functional T wave changes also commonly occur during later convalescence after mild myocarditis,[18 19] as observed also in the present series. In fact, Taggart and co-workers[13] have reported that the mechanism of the "vasoregulatory" T wave changes is an increased sensitivity of the heart to sympathoadrenergic drive instead of an increased level of circulating catecholamines. Acute myocarditis would thus be one sensitising factor.

SERUM ENZYMES

This clinical series of acute mild myocarditis is the first documentation of the release of abnormal amounts of CK MB enzyme in a group of patients. This finding indicates acute myocardial damage. Notably, this occurred at the very initial stage of an acute infection complicated by myocarditis. In the myopericarditis patients, the enzyme leak occurred only during the early phase of the ST segment elevations. The acute myocardial damage in the myopericarditis patients is further disclosed by echocardiographic evidence of clear-cut local myocardial contraction abnormalities.[8] In myocarditis, the enzyme increases remained smaller than those in acute myocardial infarction, while the release may be somewhat more prolonged, up to six days (Fig. 6 and 7).

Our findings indicate that in mild acute myocarditis the presence and perhaps degree of myocardial damage can be estimated by serial CK MB determinations; most clearly in patients with ST segment elevations (in 70% of the patients). In patients with myocarditis without an initial ST segment elevation,

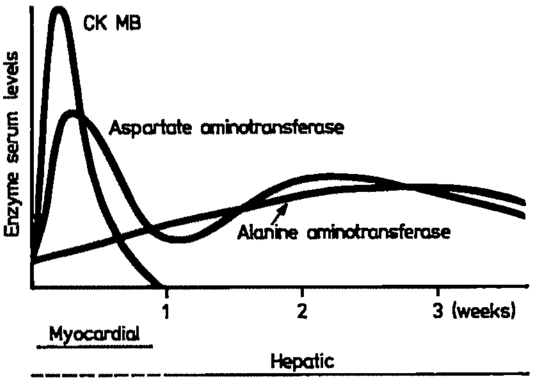

Fig. 7 *Characteristic enzyme patterns in viral myocarditis patients. The initial rises indicate myocardial enzyme release. The later secondary peak of aspartate aminotransferase coincides with a rise of alanine aminotransferase, probably indicating persistence of simultaneous hepatic involvement.*

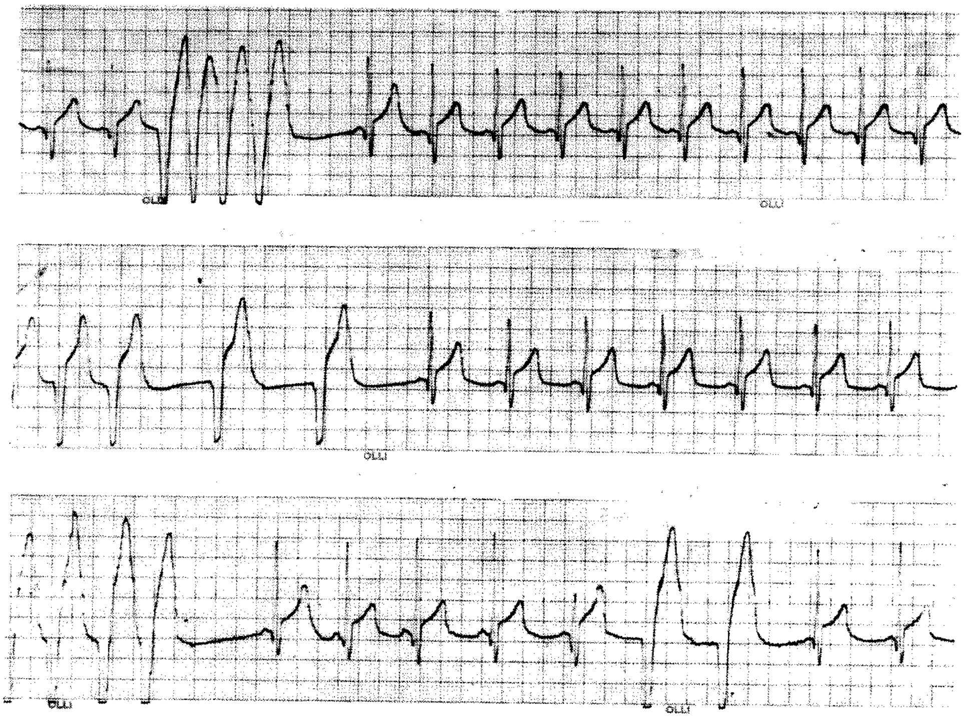

Fig. 8 *Repetitive bursts of ventricular tachycardia in a patient with acute myopericarditis. He had severe pericarditis-type chest pains but did not feel any cardiac irregularity. Tachycardias disappeared in two days with procainamide which was administered for one week. CK MB value was 186 IU/l.*

the serum CK MB increased in only 10% of the patients, probably indicating only minor myocardial pathology. In addition to an increase in CK MB, the serum aspartate aminotransferase is often also increased in patients with myopericarditis, again at the initial stage of ST segment elevation. High values, however, were often noted at the later stage as well, when CK MB was normal. In these patients there was always a simultaneous increase in alanine aminotransferase, the obvious cause being hepatocellular damage (Fig. 7). Thus, viral myocarditis may often be accompanied by slight hepatitis, a well-known example being infectious mononucleosis.

On the basis of these data we propose that enzyme diagnostics be performed serially at the very initial stage of suspected myocarditis, as is the case with patients with acute myocardial infarction.

CLINICAL CORRELATIONS AND IMPLICATIONS

The general view is that myopericarditis usually develops one to two weeks after the onset of an acute respiratory infection.[20] The close follow-up of most patients in our series, however, clearly indicates that clinical, electrocardiographic, myocardial enzymatic, and echocardiographic signs of myocardial involvement are present from the first days of a viral infection. In the majority of the patients, myocardial damage was local. This course of the disease reflects a direct and often local viral invasion of the myocardium,[1 21] instead of immunopathogenetic mechanisms. Certainly, the latter mechanism may contribute later to a persisting disease state in some patients.[1 4] Further, mild myocarditis was usually completely cured in a few weeks to months.

In our experience, the characteristic electrocardiogram of "acute pericarditis" seems to reflect the very initial stage of myocarditis. In fact, our data indicate that myocardial damage in viral myopericarditis seems to be the basic pathology, not "isolated" pericarditis. In the presence of pericarditis the diagnosis of underlying myocarditis may be overlooked; the latter is suggested by the presence of clinical and echocardiographic ventricular asynergy, S_3 gallop, subsequent local T wave inversions, and early enzyme release. The concomitant pericarditis may actually be a secondary irritation of the subepicardial myocardial lesion, as is the case in acute myocardial infarction.

Even in mild acute myocarditis serious cardiac arrhythmias, that is atrioventricular block or ventricular tachycardia, are possible. These arrhythmias may predict sudden death in myocarditis. Though rare,[3] this possibility of a serious complication warrants the careful observation of these patients during the first days of the disease (Fig. 8), and an avoidance of physical exercise during this period.[22]

The patients in this study population recovered quickly, with only a few exceptions. In reports of similar patients, the long-term prognosis is good.[18 19] The pathogenesis of severe and fatal myocarditis, leading to intractable heart failure and pronounced histological inflammatory changes,[4 23 24] seems to be different from that of acute mild myocarditis. Continuing long-term clinical and echocardiographic follow-up will reveal if any of these patients with mild myocarditis will later develop chronic congestive cardiomyopathy.

The use of corticosteroids has aggravated experimental viral myocarditis.[25] Corticosteroids would therefore be contraindicated in the acute stage of viral uncomplicated myocarditis. Instead, other non-steroidal anti-inflammatory drugs can be used successfully and more safely to relieve pericardial pain. We did not use steroids in this series, and neither did we see progressive deterioration of cardiac involvement.

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Echocardiographic detection of subvalvar aortic root aneurysm extending to mitral valve annulus as complication of aortic valve endocarditis

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SUMMARY Acute aortic regurgitation as a consequence of infective endocarditis developed in a young man after peritonitis. A large subvalvar aortic root aneurysm extending to the mitral valve annulus together with features of severe acute aortic regurgitation were shown by M-mode echocardiography. The echocardiographic findings were confirmed at operation when obliteration of the aneurysmal space and aortic valve replacement were performed. Postoperative echocardiography confirmed obliteration of the aneurysmal space.

Subvalvar aortic aneurysms initially thought to be of congenital origin and virtually confined to African Negroes may occur as a complication of aortic valve endocarditis.[1–5] Until recently subvalvar aortic aneurysms could only be detected preoperatively by aortography. Recent case reports have shown that these aneurysms may be detected by M-mode echocardiography.[6–8] The subvalvar aneurysms detected, however, did not extend to the mitral valve annulus and only in one case could endocarditis be definitely implicated as the cause.

Mycotic aneurysms involving the region of the left ventricular outflow tract are an indication for early surgical treatment. In the present case M-mode echocardiography clearly showed the subvalvar aneurysm extending to the mitral valve annulus. This finding was confirmed at operation. Careful M-mode echocardiography provides a non-invasive means of diagnosing these aneurysms in the critically ill patient without resorting to cardiac catheterisation.

Case report

A 19-year-old student with no previous cardiovascular history was admitted to a hospital in Amsterdam with acute peritonitis. An emergency laparotomy showed a perforated appendix and 500 ml pus was drained from the abdominal cavity. Despite antibiotic treatment with gentamycin, metronidazole, and carbenicillin a grumbling fever persisted. Eleven days later a second laparotomy was performed and two large abscess cavities in the left subphrenic space and pouch of Douglas were found. The abscess cavities were drained and antibiotic therapy continued until his discharge. Two days later he was admitted to Papworth Hospital with increasing shortness of breath and night sweats. On admission he was severely ill in pulmonary oedema and with cardiovascular signs of severe acute aortic regurgitation. He was afebrile and had no stigmata of infective endocarditis. Blood cultures remained sterile. Echocardiography disclosed a large echo-free space posterior to the posterior aortic wall (Fig. 1A) extending to the mitral valve annulus (Fig. 1B). Presystolic mitral valve closure indicated severe acute aortic regurgitation[9] (Fig. 2A). Open heart surgery was performed three weeks after his admission to Papworth Hospital and 10 weeks after his initial presentation with acute appendicitis. A large subaortic annular aneurysm was found between the aortic annulus anteriorly and the left atrium posteriorly. The mouth of the aneurysm occupied an area from the middle of the non-coronary sinus to the middle of the left coronary sinus and buried downwards and posteriorly leading to detachment of the mitral valve annulus. The aneurysmal sac contained infected granulations. The aortic valve was tricuspid with a large perforation in the non-coronary cusp—the prime cause of the regurgitation. A strip of pericardium was used to line the outflow tract of the left ventricle and the mitral valve was reattached. The aneurysm was obliterated by interrupted sutures and

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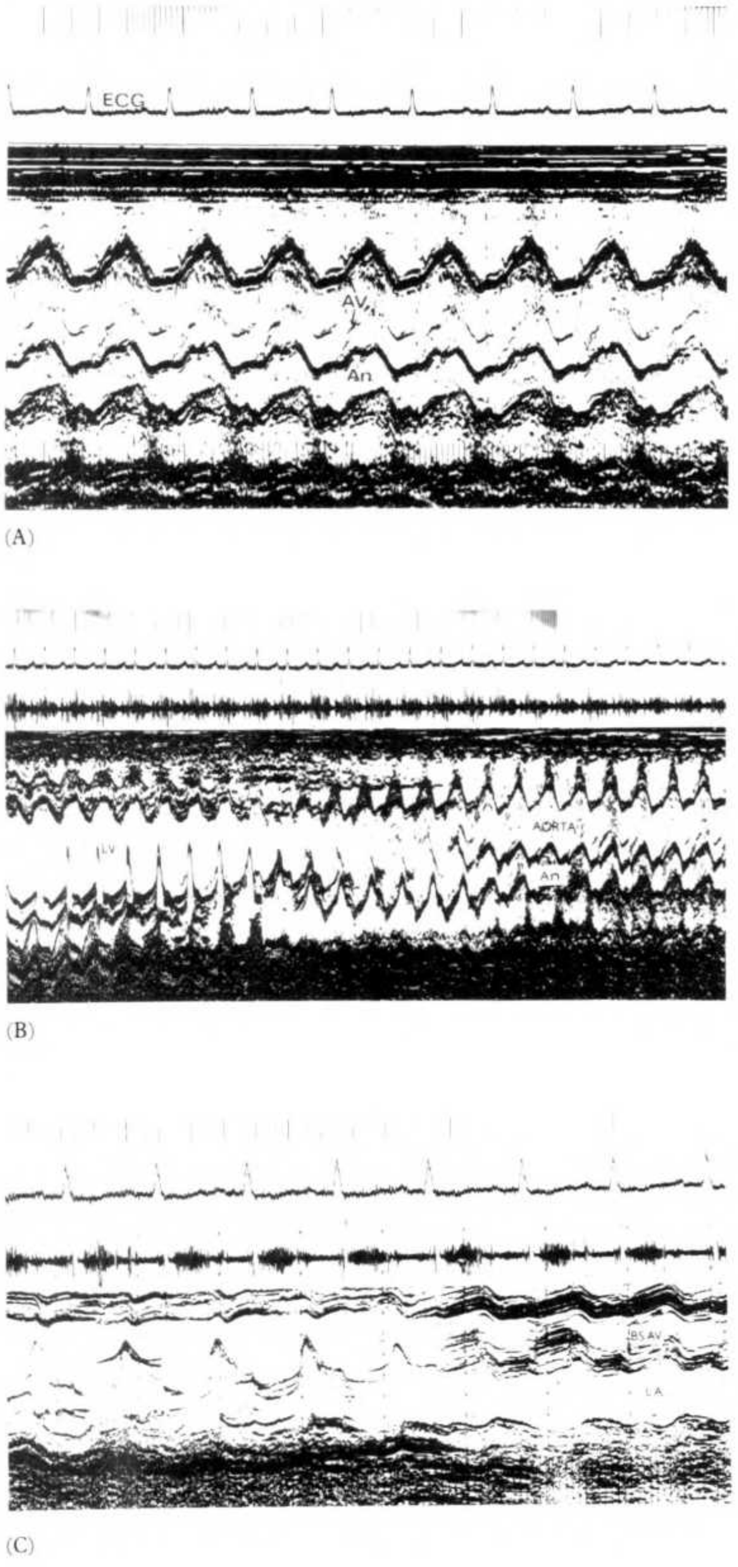

Fig. 1 *(A) Preoperative echocardiogram of aorta and aortic valve showing a large aneurysm (An) as an echo-free space posterior to the aorta and anterior to the left atrium. The aneurysm expands in late diastole and early systole and narrows in early diastole.*
(B) Preoperative echocardiogram LV aorta scan illustrating the posterior aneurysm extending to the mitral valve annulus. Vigorous contraction of the septum and left ventricular posterior wall suggests severe aortic regurgitation.
(C) Postoperative echocardiogram LV aorta scan showing obliteration of the aneurysmal space, with thickening of the posterior wall secondary to fibrosis within the obliterated aneurysm. AV, aortic valve; LV, left ventricle; BSAV, Björk-Shiley aortic valve; LA, left atrium.

the aortic valve excised and replaced with a No. 21 Björk-Shiley prosthesis.

Postoperative echocardiography confirmed obliteration of the aneurysmal space (Fig. 1C) with thickening of the posterior aortic wall secondary to thrombosis and fibrosis within the obliterated aneurysm and normalisation of mitral valve closure (Fig. 2B). The patient has subsequently remained well but with residual haemodynamically insignificant mitral and aortic regurgitation.

Discussion

Subvalvar aortic aneurysms initially considered congenital in origin and virtually confined to African Negroes are now a recognised complication of infective endocarditis and may be encountered in up to 10% of patients undergoing aortic valve replacement for aortic valve endocarditis.[1–5 10] Trauma is another precipitating cause.[11] The special problems and surgical treatment involved in such patients have been discussed by Gonzalez-Lavin *et al.*[10] The left ventricular outflow tract is a region of strategic importance.[12] Here the mitral-aortic intervalvular fibrosa connects the part of the aortic root related to the non-coronary and left coronary aortic valve cusps to the base of the anterior mitral valve leaflet. Wedged between the aorta and adjacent left atrium and extending to the intervalvular fibrosa is epicardial tissue—the epicardial wedge. Infection from the aortic valve may therefore spread directly to the epicardial wedge which itself has little resistance to infection because of its relative avascularity[13] and thus lead to aneurysm formation.[14] Infection may similarly extend to the anterior mitral valve leaflet. Because of this particular anatomical relation infection may reach the mitral valve in another way. The anterior mitral valve leaflet lies immediately subjacent to the aortic valve and may become secondarily infected by regurgitation of blood through an actively infected aortic valve—the "jet lesion".[15 16]

Pneumococcal and staphylococcal infections are the

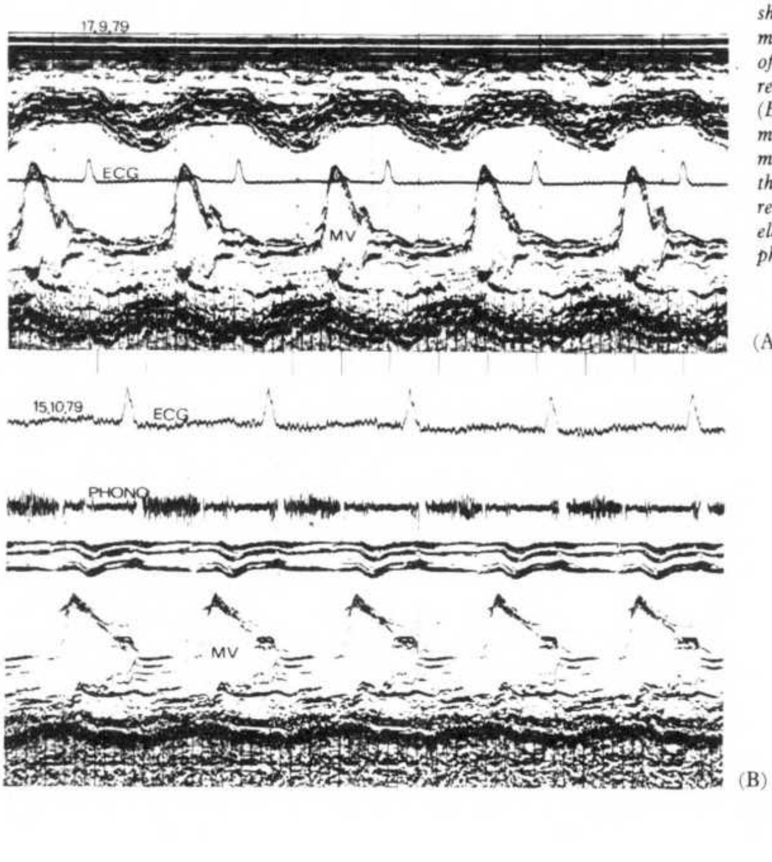

Fig. 2 *(A) Preoperative echocardiogram of the mitral valve showing almost complete closure of the mitral valve 60 ms before the inscription of the QRS complex of a simultaneously recorded electrocardiogram.*
(B) Postoperative echocardiogram of the mitral valve showing normalisation of mitral valve closure after the inscription of the QRS complex of a simultaneously recorded electrocardiogram. ECG, electrocardiogram; PHONO, phonocardiogram; MV, mitral valve.

most common organisms,[5] though cases secondary to fungi[10,17] and *Brucella suis*[18] infection have been reported. Indeed, *Brucella suis* was implicated in the first recorded case of a subannular aneurysm secondary to infection.[18]

These aneurysms may calcify,[8,10] thrombose, and subsequently embolise,[19] extend and rupture into a chamber of the right heart,[4] lead to aortic regurgitation secondary to distortion of the aortic valve,[6] rupture into the pericardium with subsequent death because of haemopericardial tamponade,[14,20,21] extend to the mitral valve annulus with detachment of the mitral valve,[10] or extend to the interventricular septum.[7] Their presence usually indicates early surgical referral and treatment.

Until recently aortography was the only means of establishing preoperative diagnosis. Despite a recent paper disputing the dangers of cardiac catheterisation in patients with infective endocarditis,[22] cardiac catheterisation is not without its risks when performed in acutely ill patients with aortic valve endocarditis.[23–25] A non-invasive method of diagnosing these aneurysms is clearly desirable.

Three recent case reports have shown the usefulness of M-mode echocardiography in the detection of subannular aneurysms.[6–8] In none of these reported cases, however, did the detected aneurysm extend to the mitral valve annulus and a recent infective process (*Staph. aureus*) could only be implicated in one case.[7]

The differential diagnosis of the echocardiographic features described includes a sinus of Valsalva aneurysm of the non-coronary sinus—a possible complication of infective endocarditis. A congenital sinus of Valsalva aneurysm would be extremely unlikely as they are confined almost exclusively to the right coronary sinus[26] and would occupy a position anterior to the anterior aortic wall.[27] In this case the diagnosis of infective endocarditis can be in no doubt: the development of acute regurgitation after a prolonged febrile episode, and the presence of infective granulations containing degenerative cocci in the aneurysm support the diagnosis.

Preoperative echocardiography detected the large annular aneurysm and its extension to the mitral valve annulus. Echocardiography also clearly showed the severity of the aortic regurgitation, with features of left ventricular volume overload and presystolic closure of the mitral valve. Cardiac catheterisation was not performed in this ill young man. The echocardiographic findings were confirmed at operation.

We conclude that M-mode echocardiography may provide valuable information in patients with severe aortic valve endocarditis and may show subannular aortic aneurysms when present. Careful echocardiography may obviate the need for cardiac catheterisation in the critically ill patient.

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Notice

Subacute bacterial endocarditis

A survey is currently being carried out by the British Cardiac Society and the Medical Services Study Group of the Royal College of Physicians. Though improvement of dental prophylaxis is one objective, the survey is already yielding other valuable information. It is hoped that proformas will be received in respect of a high proportion of patients with subacute bacterial endocarditis in the British Isles seen during 1981 and 1982 and readers are asked to arrange for them to be submitted in respect of any cases that come to their notice. Proformas can be obtained from Sir Cyril Clarke, Medical Services Study Group, King's Fund Centre, 126 Albert Street, London NW1 7NF (tel. 01-267 6111, ext. 263) to whom they should be returned.

Br Heart J 1982; 47: 397–9

Detection of intracardiac thrombi in a case of cardiomyopathy by two dimensional echocardiography

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SUMMARY A case of cardiomyopathy with systemic emboli is reported. Two dimensional and M-mode echocardiography showed abnormal intracavitary echoes. After further systemic emboli, echocardiograms showed the complete disappearance of the abnormal echoes found previously in the apex, which suggested that the emboli resulted from detachment of the left ventricular mural thrombi.

Intracardiac mural thrombi are frequently associated with ventricular hypokinesia such as occurs in myocardial infarction and cardiomyopathy.[1 2] Most of these thrombi are discovered during necropsy and are difficult to detect clinically. We describe the two dimensional and M-mode echocardiographic features of left ventricular thrombi which were found in a case of congestive cardiomyopathy, and which disappeared completely after they became detached as systemic emboli.

Case report

An 8-year-old girl was admitted to Wakayama National Hospital in February 1980, with orthopnoea and right sided weakness. Two weeks before being admitted she had had an influenza type illness and had experienced increasing cough and shortness of breath, which seemed worse at night. Previously, when 3 years old, she had had an operation for persistent ductus arteriosus. Her elder brother had died of malignant hypertension at 6 years of age.

On examination her heart rate was 150 and the respiratory rate 45 per minute. The first and second heart sounds were normal. A third heart sound was noted at the apex. Respiration was laboured, with tachypnoea and orthopnoea. The liver was palpable 3 cm below the right costal margin. There was pitting oedema of both lower legs and feet. There was no pulsation in both radial and the right femoral arteries; there was only a weak pulsation in the left femoral and both dorsalis pedis arteries. Because of the pulse deficits the blood pressure could not be recorded. Examination of the nervous system showed a right hemiplegia, a right facial palsy, and motor aphasia.

The laboratory findings were: haematocrit 38%; the white blood cell count 22 800, with 72% neutrophils and 6% band forms, 17% lymphocytes, and 5% monocytes, blood chemistry within normal limits, erythrocyte sedimentation rate 21 mm in one hour, C-reactive protein was 4+, viral antibody titres all normal. A chest *x*-ray film showed cardiomegaly and pulmonary congestion, and an electrocardiogram showed sinus tachycardia at a rate of 150, with deep Q waves in II, III, aVF, and V2-5. The girl's congestive heart failure was treated with digitalis, diuretics, and bed rest. After five days in hospital her condition improved and the radial pulses returned to normal.

On the sixth day, however, systemic emboli occurred. The patient suddenly became unresponsive to stimuli, with conjugated deviation of the eyes to the left. The right radial artery became impalpable once more. An echocardiogram showed dilatation of the left ventricle with hypokinesia and thinning of the interventricular septum. The amplitude of movement of the mitral valve was decreased and its closure was prolonged and interrupted ("shoulder"). The left atrium, right ventricle, and aortic root were all normal.

A two dimensional echocardiogram showed abnormal echoes in the apex (Fig. 1). These abnormal echoes moved during cardiac contraction and were thought to be thrombi. They were not at first detected on M-mode echocardiography but as the transducer was rotated from the base toward the apex of the left ventricle, additional intracavitary densities were seen

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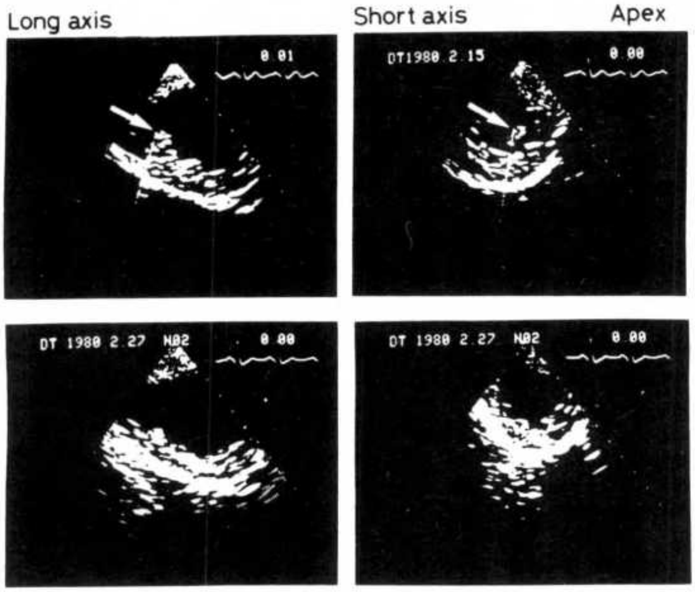

Fig. 1 *Two dimensional echocardiograms before (upper) and after (lower) systemic embolisation. Mural thrombus (arrows) is shown in the apex, which disappeared completely after systemic embolisation.*

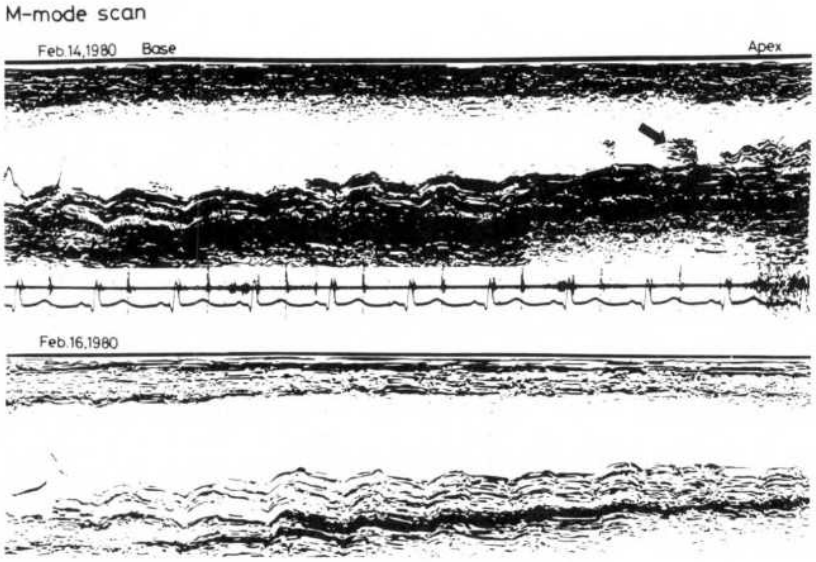

Fig. 2 *M-mode echocardiograms before (upper) and after (lower) systemic emboli had occurred, showing a mass of echoes (arrow) in the apical area which disappeared.*

in the apical area adjacent to the posterior wall (Fig. 2). After further systemic emboli occurred (cerebral, right radial) the M-mode and the two dimensional echocardiograms showed complete disappearance of these abnormal apical echoes (Fig. 1, 2). A CT scan on the 24th hospital day indicated a low density in the areas of the lentriculo-striate artery. This was made more distinct by the contrast method. Though motor aphasia was improved by subsequent treatment, right hemiplegia persisted.

Discussion

Left ventricular thrombi commonly occur in myocardial infarction and cardiomyopathy. Spodick and Littmann[3] found that over 50% of cases of cardiomyopathy were found at necropsy to have thrombi. Though thromboembolism occurs more frequently in older patients, Harris *et al.*[4] reported emboli in four of 10 children with cardiomyopathy.

In our case, cardiac catheterisation was not performed because left ventriculography is dangerous in cases with mural thrombi and this is especially true in children. Our patient had no past history suggesting myocardial infarction or the mucocutaneous lymph node syndrome. Therefore, congestive cardiomyopathy was diagnosed. After systemic emboli had occurred, abnormal intraventricular echoes suggested mural thrombi and these disappeared when further emboli occurred.

Thrombi often occur in the left atrium and the value of echocardiography in diagnosing these is well known,[5 6] but the reliability of echocardiography in detecting left ventricular thrombi has not been fully assessed. Horgan *et al.*[7] reported a left ventricular thrombus detected by M-mode echocardiography. Subsequently, Kramer *et al.*[8] described a patient with alcoholic cardiomyopathy with left ventricular mural thrombi.

Horgan *et al.*[7] stated that a thrombus must be both large and organised in order to be detected by echocardiography. Though some authors have reported that M-mode echocardiography is a useful technique in detecting intracavitary thrombi, it is less useful in demonstrating mural thrombi. Ports *et al.*[9] reported that both intracavitary and intramural left ventricular tumour masses were detected with M-mode and two dimensional echocardiography. M-mode echocardiography, however, did not show a ventricular thrombus in all instances.[9] Two dimensional echocardiography easily identified the large and inhomogeneous left ventricular thrombi, but it could not always clearly show smaller mural thrombi.

In our case, intraventricular mural thrombi were directly visualised and their location, size, and subsequent movement were detected with two dimensional echocardiography, which was therefore valuable.

We wish to thank Drs Kozo Takenaka and Shinji Mikita for their valuable advice in this case.

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A case of isolated atrioventricular discordance

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SUMMARY A case of isolated atrioventricular discordance in situs solitus is described.

The importance of a well defined situs and of the presence of both ventricles in making this diagnosis is underlined and previous published reports reviewed.

It is suggested that the haemodynamic concept of isolated atrioventricular discordance cannot be described only by the spatial relation between the ventricles (isolated ventricular inversion), but it should be indicted by the pattern of the connection between various flows, as shown by hearts with a normal relation between the ventricles and crossed atrioventricular connection.

We consider that "A-V discordance with ventriculo-arterial concordance and normally related great arteries"[1] is the best way to describe the anatomical and the haemodynamic pattern in so called isolated ventricular inversion.

In this paper we report a new example of this rare anomaly which we call "isolated atrioventricular discordance". To our knowledge, this is the first reported case in which a straddling left atrioventricular valve was present.

Case report

A 2-month-old female infant (birthweight 2·5 kg) was admitted with dyspnoea and cyanosis which had been present from birth.

A xiphoid impulse was present and a grade 3/6 harsh early and mid-systolic murmur was heard at the left lower sternum; the second heart sound was normal. The peripheral pulses were diminished and the liver was much enlarged. Chest *x*-ray film showed a left cardiac apex, cardiomegaly, and increased pulmonary flow. The electrocardiogram showed normal sinus rhythm, left atrial enlargement, and a QRS axis at +140° in the frontal plane. An RS pattern in all the praecordial leads was present. The vectorcardiogram showed a figure-of-eight inscription in the frontal plane with clockwise rotation and inferior and leftward directed initial forces; in the horizontal plane, counterclockwise rotation was present, with most of the loop in the posterior and right quadrant. The 0·01^s vector was oriented anteriorly and to the left.

ANATOMICAL DESCRIPTION

Laevocardia and solitus visceroatrial situs were present, with normal atrial morphology and the normal relation between the atrial chambers. Systemic and pulmonary connections were normal. The atrioventricular connection was discordant with two separated atrioventricular valves, the left of which was straddling. The right atrium was connected to a right sided and morphologically left ventricle through a bicuspid valve (Fig. 1A). The subvalvular apparatus was normal. A normal-sized ventricle was connected to a right sided and posterior aorta (Fig. 1B). Fibrous continuity between the anteromedial leaflet of the right atrioventricular valve and the aortic cusps was documented. A fibromuscular membrane obstructing the aortic outflow tract was present (Fig. 1B). The ventricular septum was abnormally orientated, so that its posterior aspect was to the left of its anterior aspect; a perimembranous ventricular septal defect was present (Fig. 1B). Some chordae from the left atrioventricular valve had their insertion on the base of the septal defect on its right side. The left atrium was connected to a left sided, morphologically right ventricle through a tricuspid valve (Fig. 2A). The normal sized atrioventricular valve annulus was shifted medially and to the right but did not override the ventricular septum. The anterior leaflet of the left tricuspid atrioventricular valve had its insertion on the anterior papillary muscle and on the left side of the septum by some chordae tendineae. The posterior leaflet had its insertion on two posterior papillary muscles. The septal leaflet inserted directly on the septum with some chordae tendineae on the left side, and some, through the ventricular septal defect, on the right side of the ventricular septum (Fig. 2A). The morphologically right ventricle was smaller than the left, had a well-developed "crista supraventricularis",

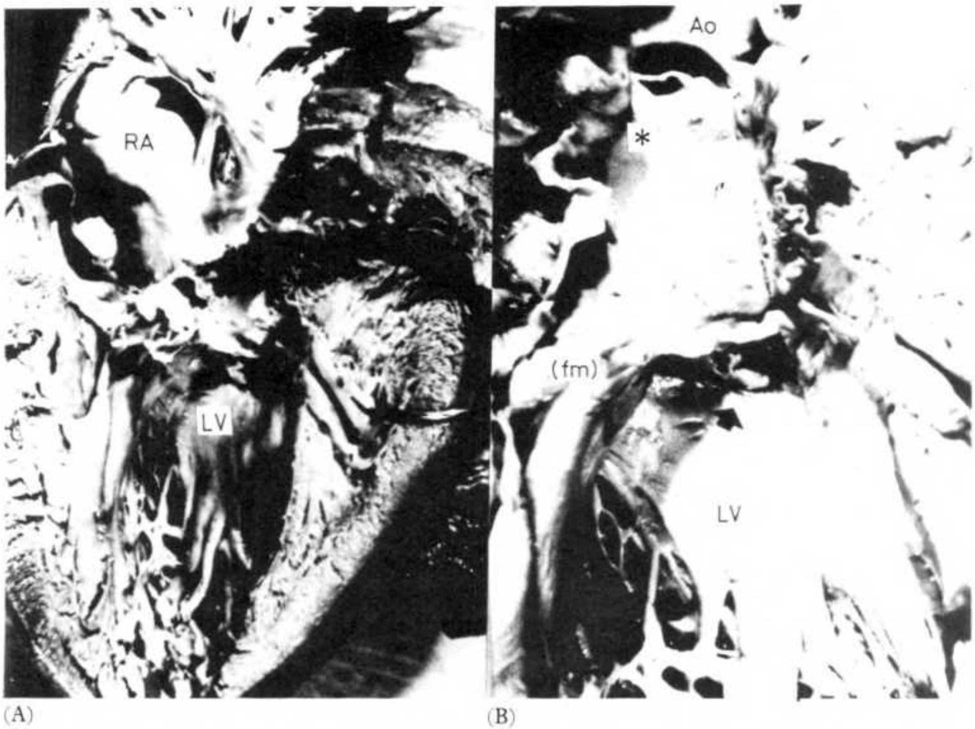

Fig. 1 *(A) Right atrioventricular connection: the right atrium (RA) is connected to a morphologically left ventricle (LV) through a bicuspid valve. (B) This ventricle is normally connected to a right sided and posterior aorta (Ao). Fibrous continuity between the atrioventricular valve and the aortic cusps (*). A fibromuscular membrane (fm) is present in the subaortic outflow tract. Through a perimembranous ventricular septal defect there are some chordae of the left sided atrioventricular valve (arrow).*

and was connected to the pulmonary artery with an infundibulum (Fig. 2B). Coarctation of the aorta and persistent ductus arteriosus were present.

Discussion

The final diagnosis in our case is: situs solitus, atrioventricular discordance, with straddling but not overriding left atrioventricular valve, left sided and anterior morphologically right ventricle, right sided and posterior morphologically left ventricle, ventriculoarterial concordance and normally related great arteries, fibromuscular subaortic stenosis, coarctation of the aorta, and persistent ductus arteriosus.

Isolated atrioventricular discordance requires the presence of a well-defined situs (solitus or inversus) and of both ventricles, regardless of their spatial relation.

In our view, some published cases of isolated ventricular inversion do not fit this description, because they are univentricular hearts,[2-4] but an isolated atrioventricular discordance is present in the other published cases described as isolated ventricular inversion,[5-8] and in Attie *et al.*'s second case reported as crossed atrioventricular connection with atrioventricular discordance and normal connection and relation between the great vessels.[9]

In fact, in isolated atrioventricular discordance, the mode of atrioventricular connection may be through two separate atrioventricular valves, one common atrioventricular valve,[8] or a criss-cross situation.[9] The relation between the two ventricles may vary. Usually the position of the ventricular septum and the relation between the two ventricles are inverted compared with the atrial situs. This is not true when a criss-cross situation is present or when the ventricular septum is horizontal, with a superoinferior relation between the ventricles. In this anomaly the ventriculoarterial connection must be concordant, with normally related great arteries.

The most frequently occurring infundibular morphology is represented by mitral aortic continuity and muscular discontinuity between the tricuspid valve and the pulmonary artery.

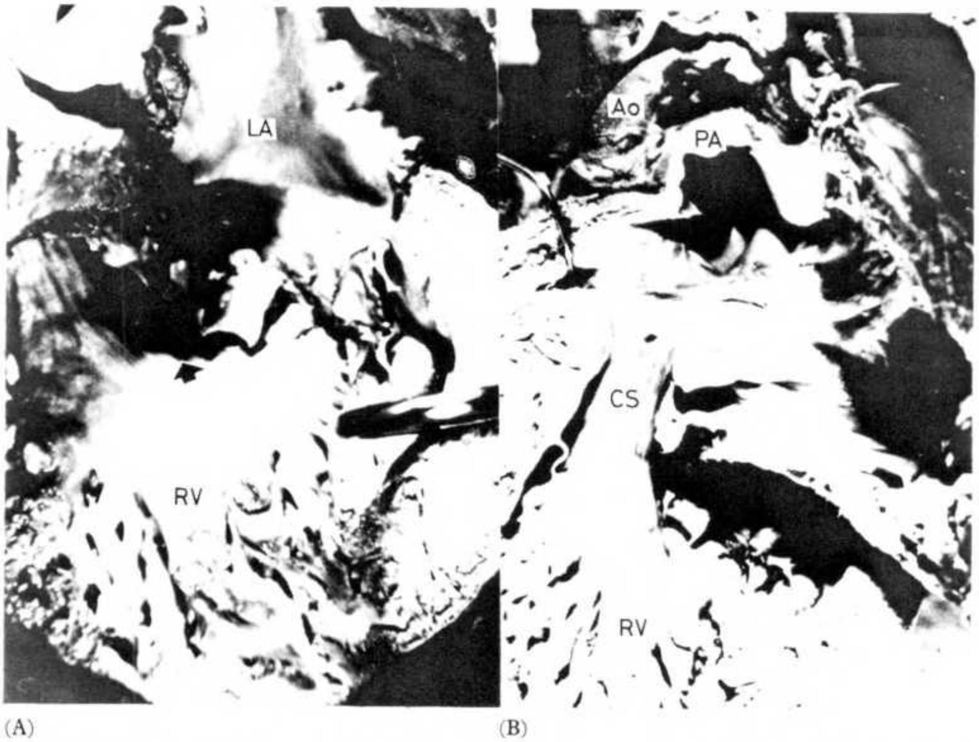

Fig. 2 *(A) Left atrioventricular connection: the left atrium (LA) is connected to a morphologically right ventricle (RV) through a tricuspid valve. Through the perimembranous ventricular septal defect the septal leaflet is inserted directly on the septum with chordae on the left and on the right (arrow). (B) The "crista supraventricularis" (CS) is well developed and a muscular discontinuity is present between right ventricle (RV) and pulmonary artery (PA).*

The most frequently associated anomalies are left atrioventricular valve (tricuspid) stenosis, with consequent right ventricular hypoplasia when situs solitus is present and right ventricular outflow tract obstruction when situs inversus is present. Other reported anomalies are ventricular septal defects of various types,[7] aortic stenosis,[5] coarctation of the aorta,[8] and persistent ductus arteriosus.[7] From a clinical standpoint, the vectocardiographic finding of anterior and leftward early vectorial forces (when situs solitus with laevocardia is present), or their anteriorly and rightward orientation (when situs inversus with dextrocardia is present), may be significant. This abnormal orientation is the result of the anomalous position of the ventricular septum.

The final diagnosis of this anomaly may be made only by cardiac catheterisation and angiocardiographic data.

We think that, in order to describe and define cardiac anomalies correctly, the intracardiac circulation should be stressed first and, then the relation between the chambers. Therefore, we suggest that the haemodynamic concept of isolated atrioventricular discordance cannot be described only by the spatial relation between the ventricles, but it should be indicated by the pattern of the connection between the various flows. This is supported by the reported cases of hearts with inverted spatial relation between the ventricles, but with crossed atrioventricular connection and, consequently, with normal circulation.[9]

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Br Heart J 1982; 47: 404–8

Myxomatous degeneration of mitral valve
M-mode and two dimensional echocardiographic findings

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SUMMARY This report presents a patient with an unusual clinical course associated with a mitral "mass" recorded by M-mode and cross-sectional echocardiography. The "mass" was confirmed at operation to be redundant myxomatous mitral valve leaflets. The problem of echocardiographic resolution in the setting of mitral valve prolapse and of the differential diagnosis of a mitral mass is discussed in detail.

M-mode and two-dimensional echocardiography are extremely useful in showing normal and abnormal mitral valve motion.[1] We report an unusual case of a patient with a mitral "mass" documented by M-mode and two-dimensional echocardiography, presenting with possible emboli from the mitral valve, who was found at surgery to have grossly flail and redundant anterior and posterior mitral valve leaflets. The importance of recognising that mitral valve prolapse can progress to flail mitral leaflets and the difficulty of documenting a true mass by M-mode as well as two-dimensional echocardiography in this setting is emphasised. The differential diagnosis is also described in detail.

Case report

The patient was a 55-year-old white man. He was well until 1940 when on physical examination he was noted to have an apical systolic murmur. He was given prophylaxis for bacterial endocarditis. The patient did well until 1964 when he noted the onset of bilateral blurred vision, which he described as "like wearing dirty glasses". The episodes lasted for approximately 45 minutes without neurological sequelae. He did well until he had two more episodes in 1969 and 1973. Ophthalmological and neurological evaluations were negative. In 1976, he had two more episodes of blurred vision—one episode was associated with slurred speech and the other with dizziness. In January 1978, the episodes of blurred vision increased in frequency to one every two weeks. He was started on acetylsalicylic acid 650 mg twice daily with resolution of his visual disturbance. Further cardiological evaluation with M-mode and two-dimensional echocardiography showed a large mass-like effect on both the anterior and posterior mitral valve leaflets; he was therefore transferred for cardiac catheterisation and consideration for mitral valve replacement. There was no history of rheumatic fever, syncope, orthopnoea, paroxysmal nocturnal dyspnoea, chills, sweats, seizures, and no family history of heart disease.

His blood pressure was 100/82 mmHg. The examination was unremarkable except for the following: the patient had a palpable systolic thrill at the apex, maximal in the left anterior axillary line. There was a grade 4/6 holosystolic murmur at the left sternal border radiating to the axilla, a diastolic sound felt to be either an opening snap or "tumour plop", and a grade 2/6 mid-diastolic rumble at the apex. There were no rubs, clicks, cyanosis, clubbing, or oedema.

Routine laboratory studies including erythrocyte sedimentation rate, Venereal Disease Research Laboratories test, rheumatoid factor, anti-nuclear factor, complement levels, protein electrophoresis, and blood cultures were all within normal limits. The electrocardiogram, vectorcardiogram, and chest *x*-ray examination demonstrated left ventricular and left atrial enlargement. The M-mode (SKF Ekoline with Irex recorder) and two-dimensional echocardiograms (Varian V 3000) showed multiple thick echoes on the posterior as well as the anterior mitral valve leaflets (Fig. 1A, 1B, 2A, and 2B).

Cardiac catheterisation disclosed a raised pulmonary artery pressure of 36/12 mmHg, with a pulmonary artery wedge V wave of 24 and a mean

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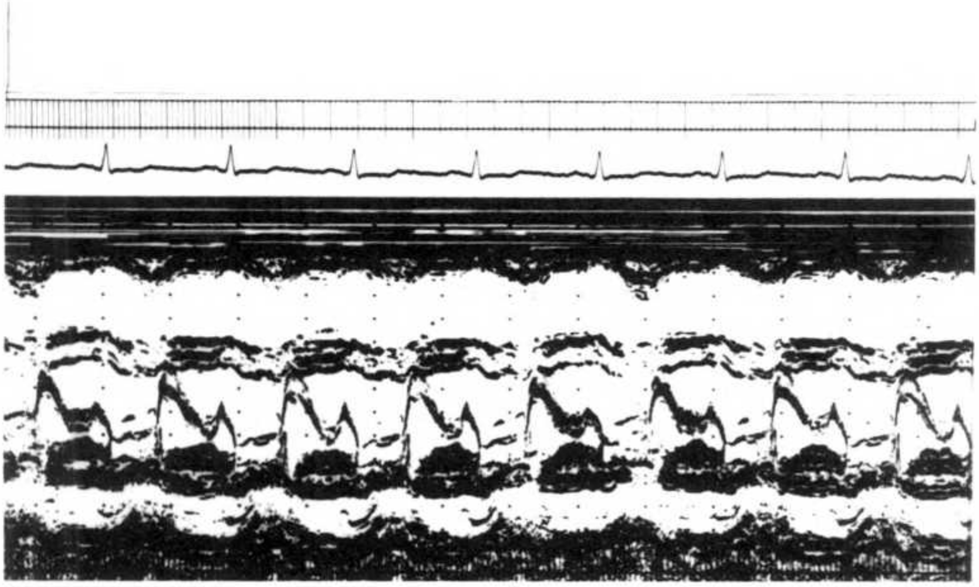

Fig. 1(A)

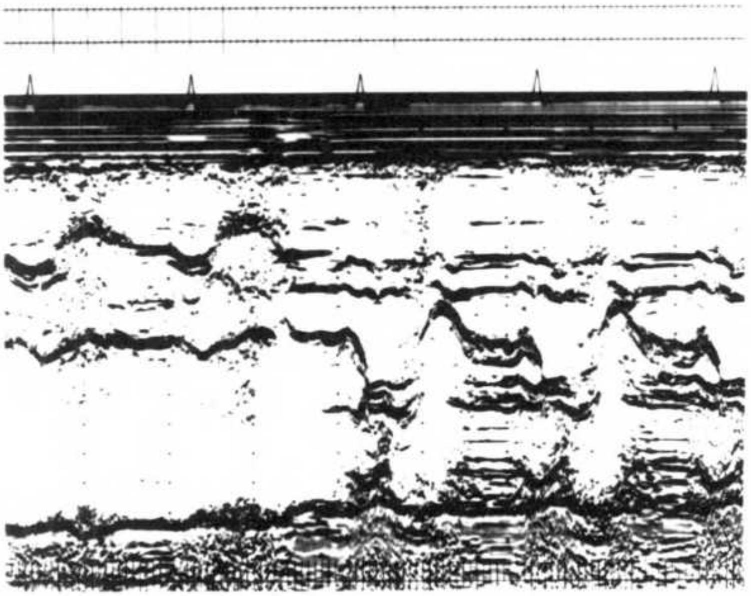

Fig. 1(B)

Fig. 1(A) M-mode echo. Continuous strip chart recording with findings of multiple thick shaggy echoes on anterior and posterior mitral valve leaflets. (B) *M-mode echo. Continuous strip chart recording with findings of systolic and diastolic fluttering, echoes displaced into left atrium during systole, dilated left atrium, hammock-like posterior bulging of posterior leaflet.*

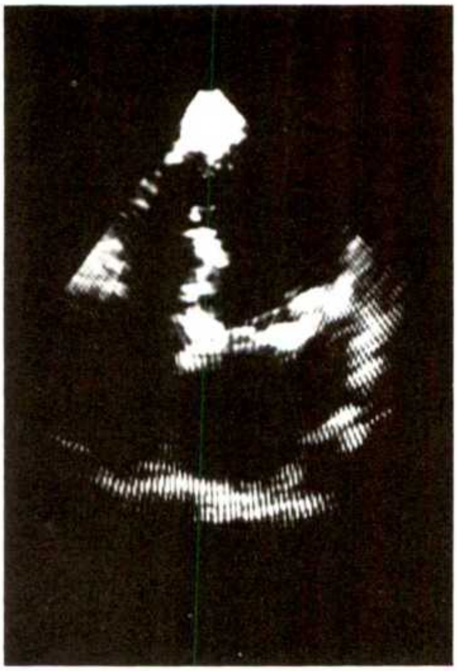

Fig. 2(A)

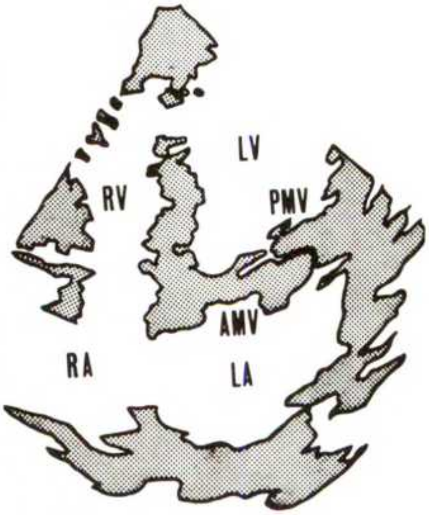

Fig. 2(B)

Fig. 2(A) *Two-dimensional echocardiogram. Masses or thickening of anterior and posterior leaflets of mitral valve in this stop-frame shot.* (B) *Two-dimensional echocardiogram outline of Fig. 2(A).*

pressure of 18 mmHg. The inferior vena cava and right atrial angiograms by hand injection were normal. Pulmonary angiography in the right anterior oblique projection showed a sizeable "mass" in the laevophase on the mitral leaflets moving back and forth into the left atrium, which was severely dilated. Coronary angiography was normal.

On 19 July 1978 during operation the patient was found to have grossly redundant anterior and posterior mitral valve leaflets without ruptured chordae tendineae. There was no evidence of thrombus, tumour, or vegetations on or around the valve. He underwent mitral valve replacement with a No. 29 Björk-Shiley valve. His postoperative course was uncomplicated. On follow-up he has done well without recurrence of his visual disturbance.

Gross and microscopical findings were as follows. The atrial appendage was normal without findings of Aschoff's bodies. The anterior and the posterior leaflets were redundant. The redundant portions were thickened, nodular, and firm with foci of mineralisation. There were histological findings of myxomatous infiltration resulting in disrupted fibrous and elastic elements. Histochemical stains disclosed an increase in acid mucopolysaccharides in the myxomatous tissue. The chordae tendineae were elongated, thin, and not fused. Rare chordal thickening disclosed an increase in acid mucopolysaccharide deposition.

Discussion

M-mode echocardiography enhances the axial evaluation of mitral valve prolapse, valvular vegetations, tumours, and flail mitral valve leaflets.[2-4] Two-dimensional echocardiography adds to the M-mode technique by providing spatial information of the lateral, superior, and inferior cardiac wall motions. Both techniques are limited, however, by gain-setting, resolution, and angulation. When two-dimensional echocardiography is studied during single frame views, there is also degradation of the image and loss of visual integration of motion.[1]

Our patient on M-mode echocardiography (Fig. 1A and 1B) seemed to manifest findings characteristic of mitral valvular vegetations as well as fibrosis and calcification. The anterior leaflet was irregularly thickened but less so than the posterior leaflet. There was a coarse mass of thick, shaggy echoes closely associated with the posterior leaflet. Evidence against vegetations was that the posterior leaflet motion appeared restricted and the valvular thickening was uniform. Furthermore, the echocardiographic presentation of a mass, density, or aggregate of echoes posterior to the anterior mitral leaflet, with displacement posteriorly into the left atrium during systole and with abrupt mid-systolic posterior motion, can also mimic a myxoma or thrombus.[5] Evidence against a myxoma or thrombus was first that the anterior cusp diastolic closure slope was normal and not decreased, and secondly that the cloud of echoes was not immediately posterior to the anterior mitral valve.

Our patient's echocardiogram also illustrates the confusion and limitations of M-mode echocardiography in patients with mitral valve prolapse.[6-9] Chandraratna and Langevin[6] found that 40% of patients with mitral valve prolapse had shaggy echoes resembling those seen in valvular vegetations. The echoes were thought to be caused by redundant leaflets presenting multiple surfaces to the transducer. The more severe the prolapse, the greater the degree of redundancy and hooding and the more echoes recorded. Without question, noninvasive localisation of a vegetation facilitates expeditious and appropriate medical and/or surgical intervention. Artefactual "vegetations" can be created by high gain settings and can be mimicked by calcification, fibrosis, and mitral valve prolapse (as demonstrated in our patient).

Humphries *et al.*[4] have reported several M-mode features of flail mitral valve leaflets or ruptured chordae tendineae also found by continuous sector scanning. These authors described paradoxical movement of the anterior and posterior leaflets during diastole, associated hammock-like posterior bulging of the posterior leaflet during systole, severely erratic early diastolic and systolic fluttering of the leaflets, with the anterior leaflet touching the intraventricular septum, abnormal systolic echoes in the left atrium moving toward the posterior left atrial wall, posterior systolic motion of the left atrium, pronounced systolic motion of the left atrium, and distinct systolic motion of the intraventricular septum. Evidence against anterior leaflet rupture in our patient was that there was no increased rate and amplitude of the anterior cusp opening and no coarse diastolic fluttering. Our patient with mitral valve prolapse did, however, present some of the echocardiographic features of a flail mitral valve. If the diagnosis of a flail mitral valve is contemplated, the timing of treatment, specifically surgery, is critical. Therefore, the accuracy of the diagnosis is imperative. Other disorders with features resembling a flail mitral valve (parachute mitral valve, Capetown valve, atrial tumour or clot, aortic regurgitation, atrial fibrillation and flutter, ventricular dysfunction, and congenital defects such as endocardial cushion defects) can be distinguished from a flail valve by other echocardiographic findings. Mitral valve prolapse, however, stands out as the exception and can be virtually indistinguishable by echocardiography.

With the advent of two-dimensional echocardiography, there was new hope of additional accuracy in the detection of vegetations, tumours, and flail mitral valve, especially in patients with mitral valve prolapse.[10 11] Our patient's two-dimensional echocardiogram (Fig. 2A and 2B) shows apparent masses or thickening on both the anterior and posterior mitral valve leaflets prolapsing in real-time into the left atrium. The apical view was specifically selected for its sensitivity in detecting the structural abnormality of the mitral valve and its apparatus. The findings were suggestive of vegetations, tumours, flail leaflets, or mitral valve prolapse. The lack of resolution by the two-dimensioal echocardiogram in delineating the multiple folds of both leaflets renders a definitive diagnosis of mitral valve prolapse difficult and indistinguishable from the other entities discussed. Future application of this technique will depend upon improving its resolution and studying its sensitivity and specificity in a large population of patients with suspected mitral valve prolapse.

Although the absolute diagnostic criteria for mitral valve prolapse have not been established, the left ventricular angiogram has been considered to be the most accurate laboratory test available, though it has limitations, especially with anterior leaflet prolapse. Our patient's angiogram in the right anterior oblique projection showed an abnormal mass or bulge moving backward into the left atrium and forward into the left ventricle. The mass or bulge projected not only anterolaterally but also anterosuperiorly, suggesting involvement of both leaflets. There was no cleft or radiolucency seen between the anterior and posterior leaflets nor any temporal dissociation between the leaflets. Furthermore, differentiation of a mass from prolapse of both leaflets by angiography was difficult for two reasons: (1) a pulmonary angiogram was done rather than a left ventricular angiogram for fear of dislodging a portion of the mass. This resulted in less contrast than necessary to visualise combined leaflet prolapse, and (2) the significant mitral regurgitation further obscured delineation of the valvular involvement.

The association of cerebral ischaemic events and prolapsing mitral valve is receiving more attention as we learn more about the natural history of mitral valve prolapse. The aetiology of our patient's transient ischaemic attacks remains unexplained though his favourable response to acetylsalicylic acid suggests a platelet embolic source, possibly emanating from his abnormal mitral valve. The gross and histological examination of his mitral valve, however, failed to show significant thrombus formation. We concur with the recommendations of Barnett *et al.*[12] that either platelet inhibitor treatment (aspirin, dypyridamole, or sulphinpyrazone) or warfarin-type anticoagulation seems to be indicated in these cases of cerebral emobli in which bacterial endocarditis has been excluded by appropriate cultures.

In summary, our patient illustrates the role of two-dimensional echocardiography versus M-mode recording in evaluating patients with mitral valve prolapse. M-mode echoes are extremely dependent on transducer angulation and resolution. Two-dimensional echoes add a spatial perspective but are also hampered by spurious echoes, dropout echoes, resolution difficulties, and overlapping echoes from transducer position.[13]

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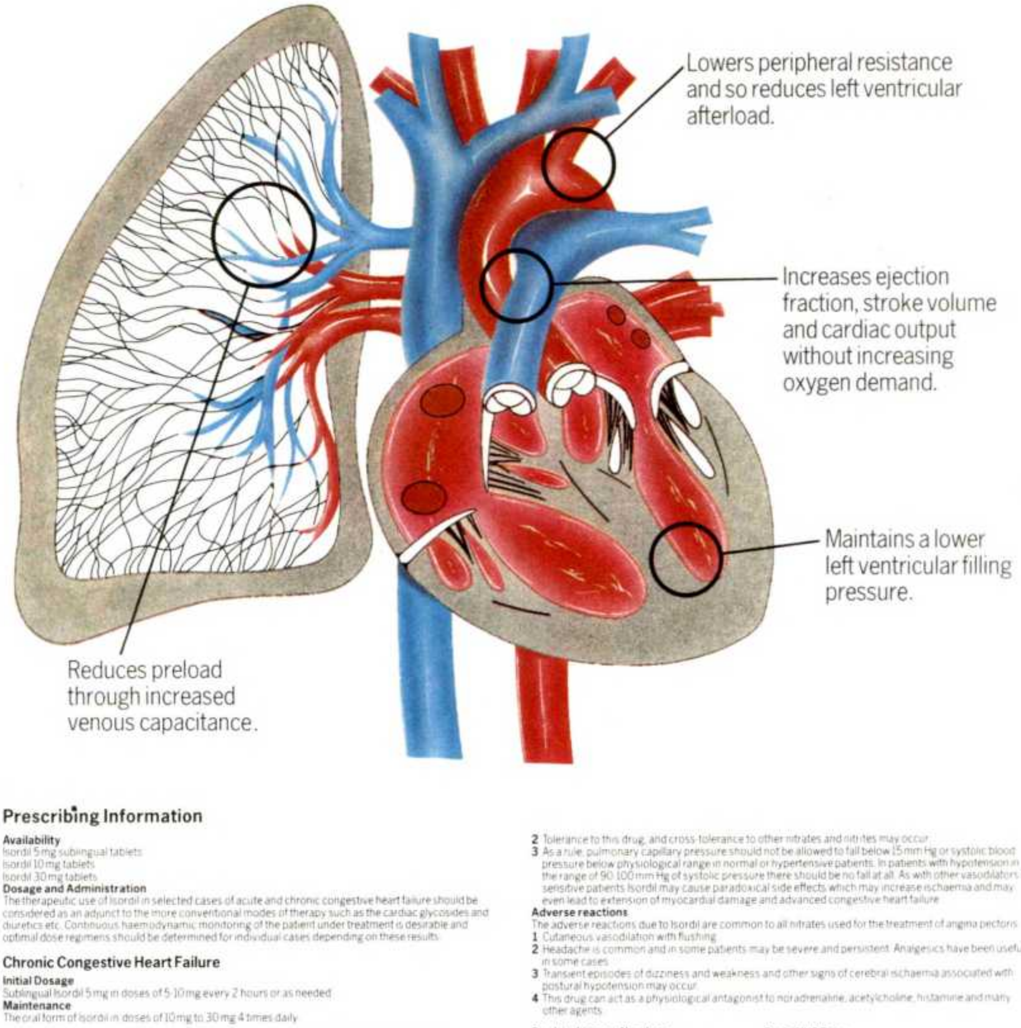

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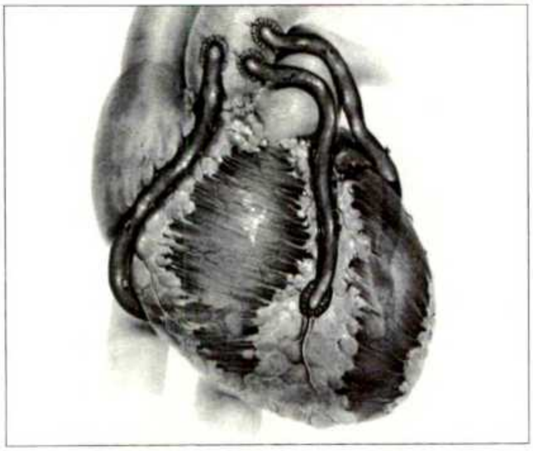

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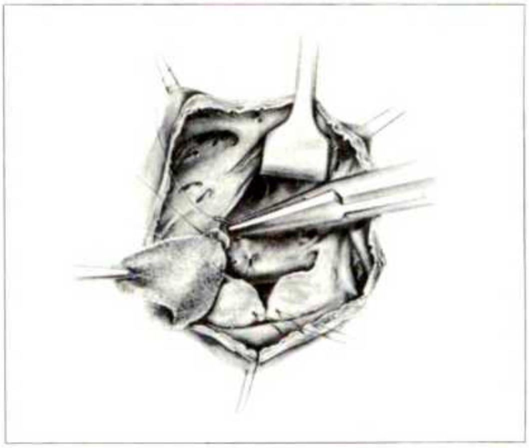

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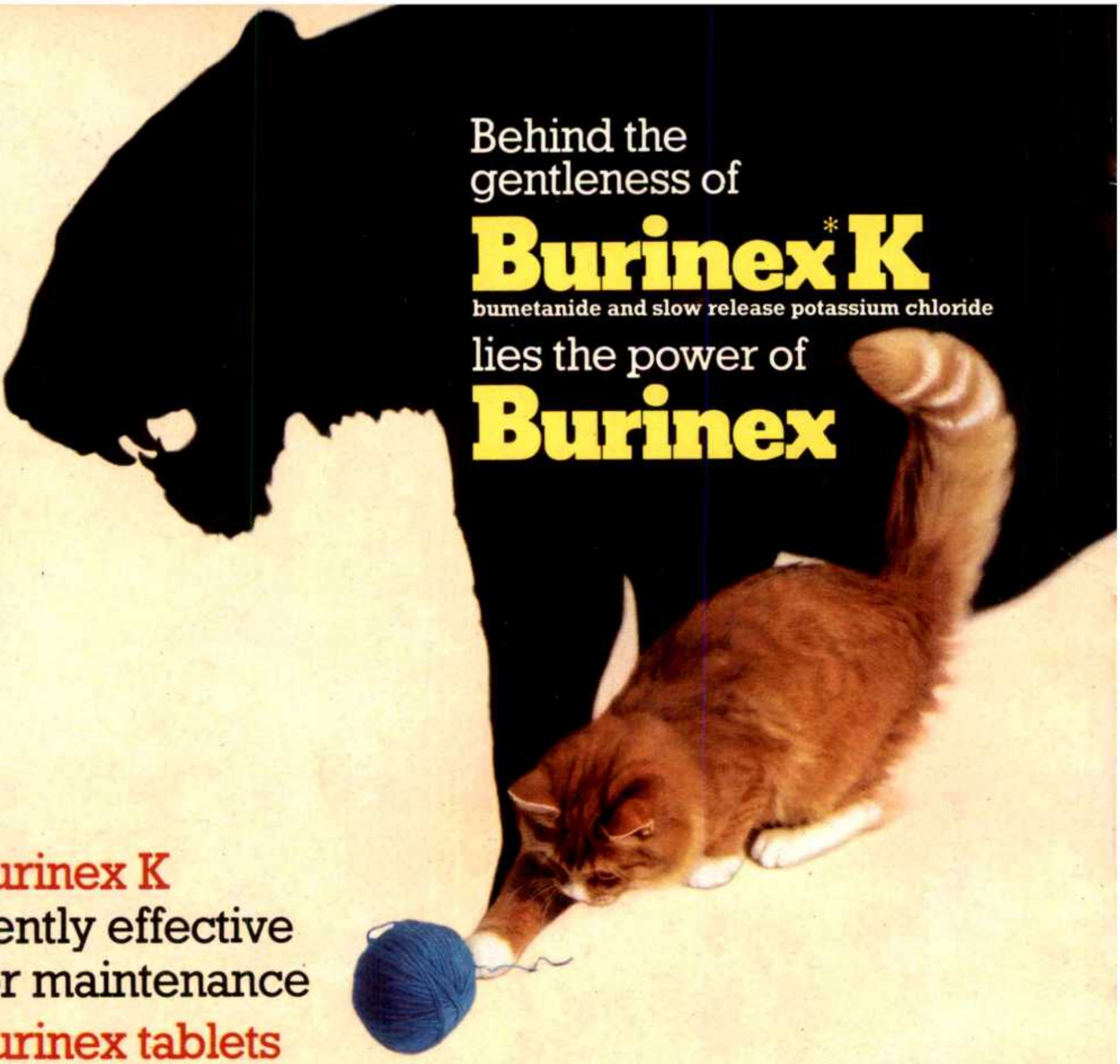

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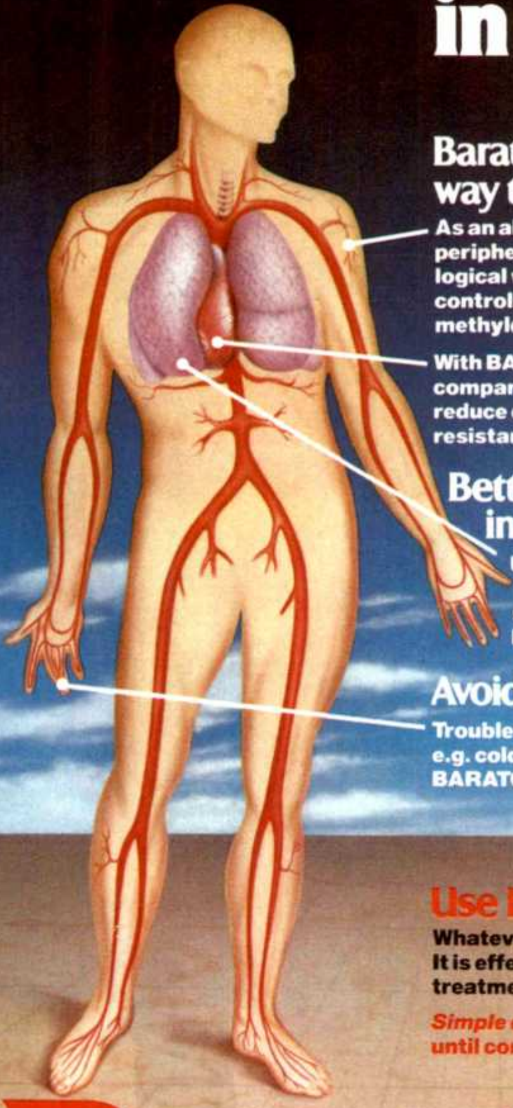

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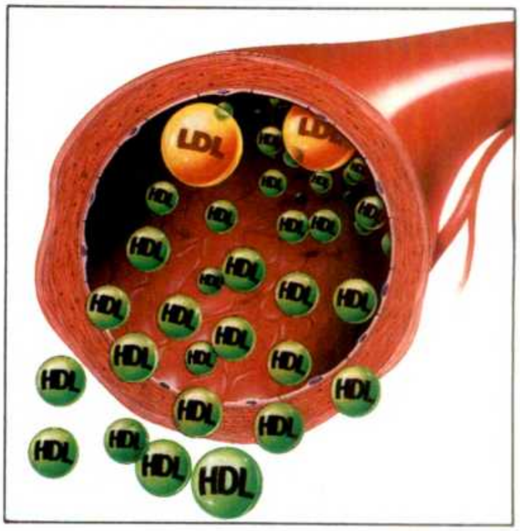

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2. Manufacturers' Literature
3. Lipoproteins and Coronary Heart Disease, Witzstrock Publishing House, New York (1980) 185-188
4. *Ibid*: 192-195
5. *Munch. med. Wschr.* **122, 5** (1980) 165-168
6. Diet and Drugs in Atherosclerosis, eds. G. Noseda, B. Lewis, R. Paoletti, Raven Press, New York (1980) 137-142

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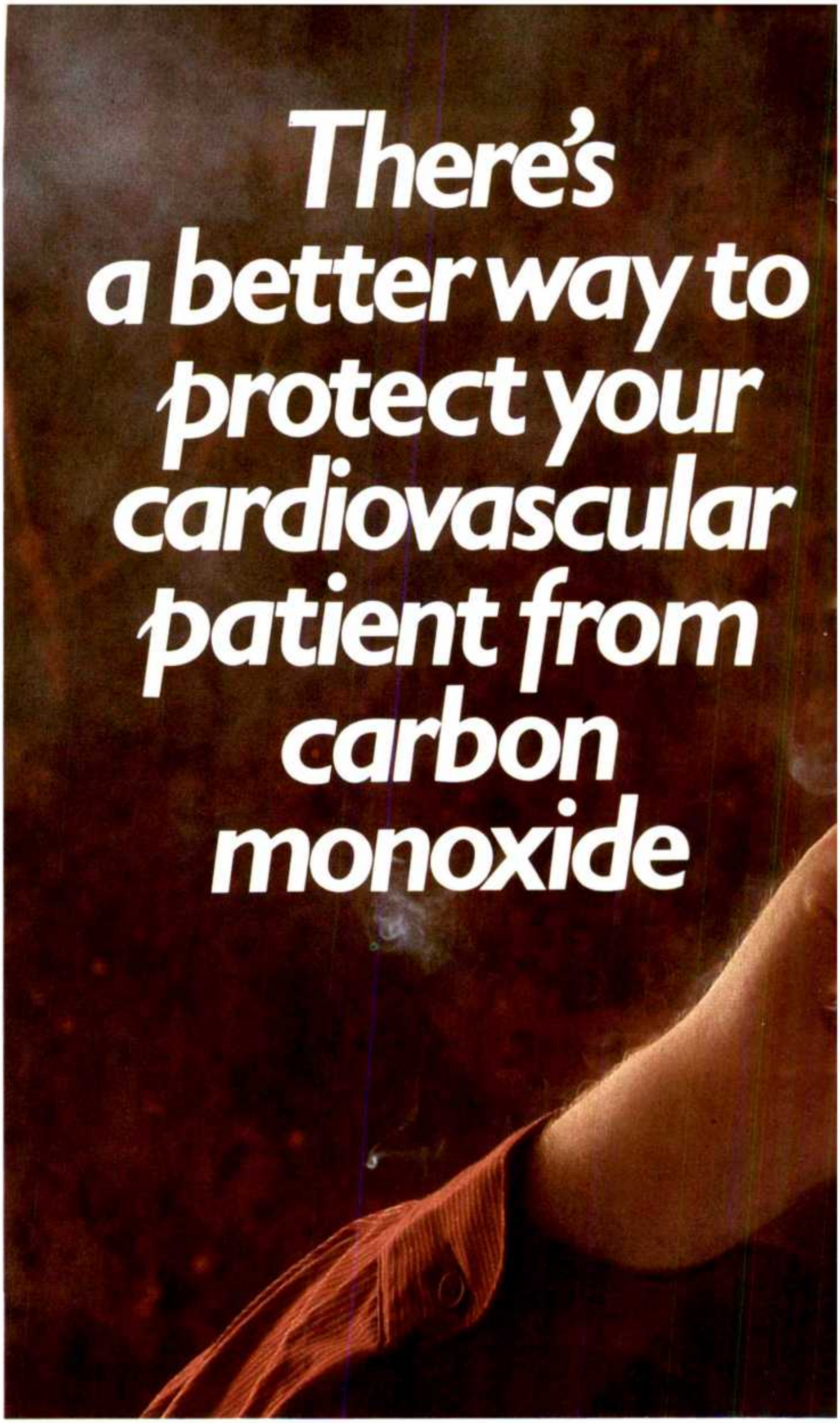
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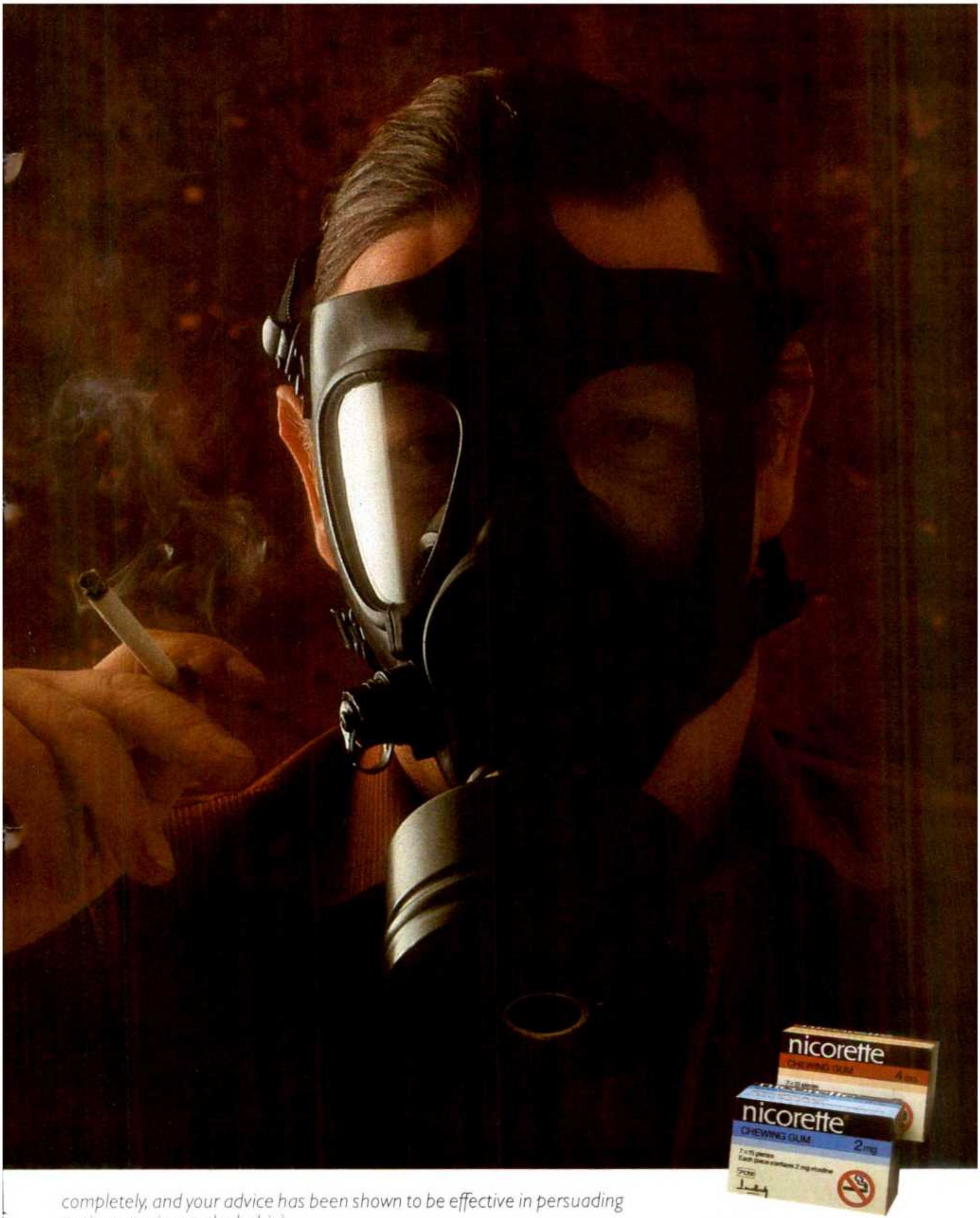

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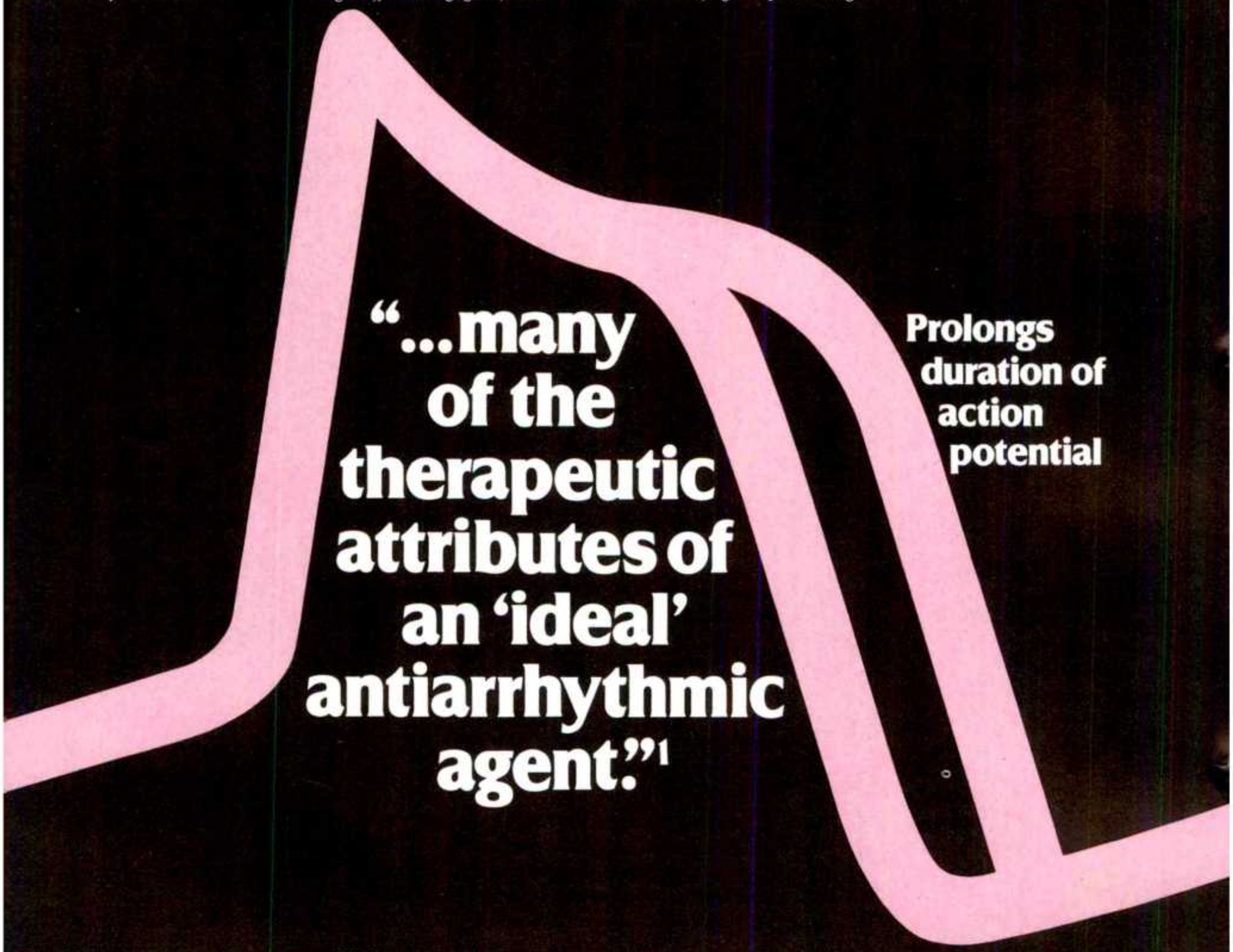

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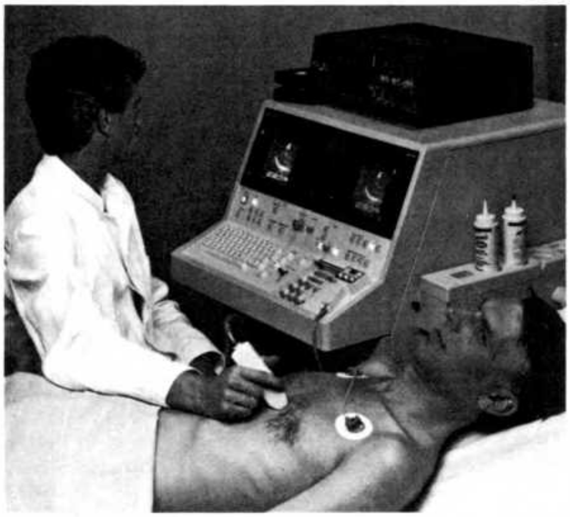

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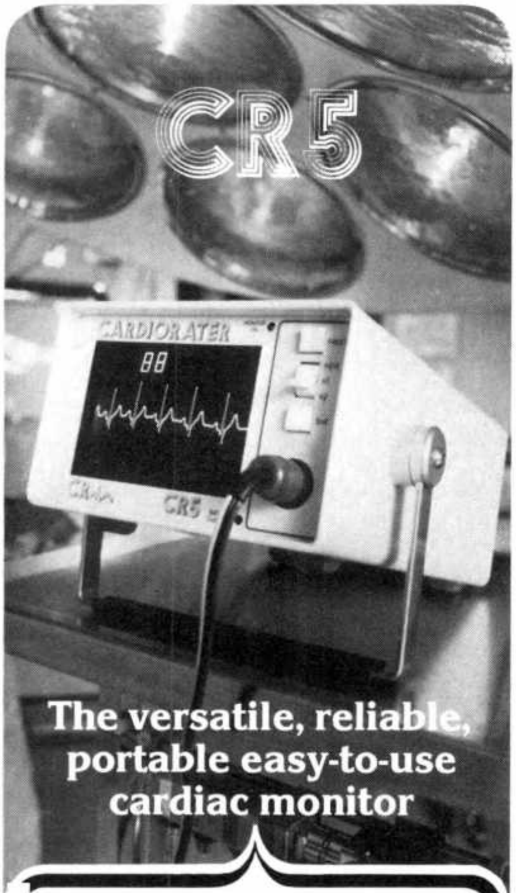
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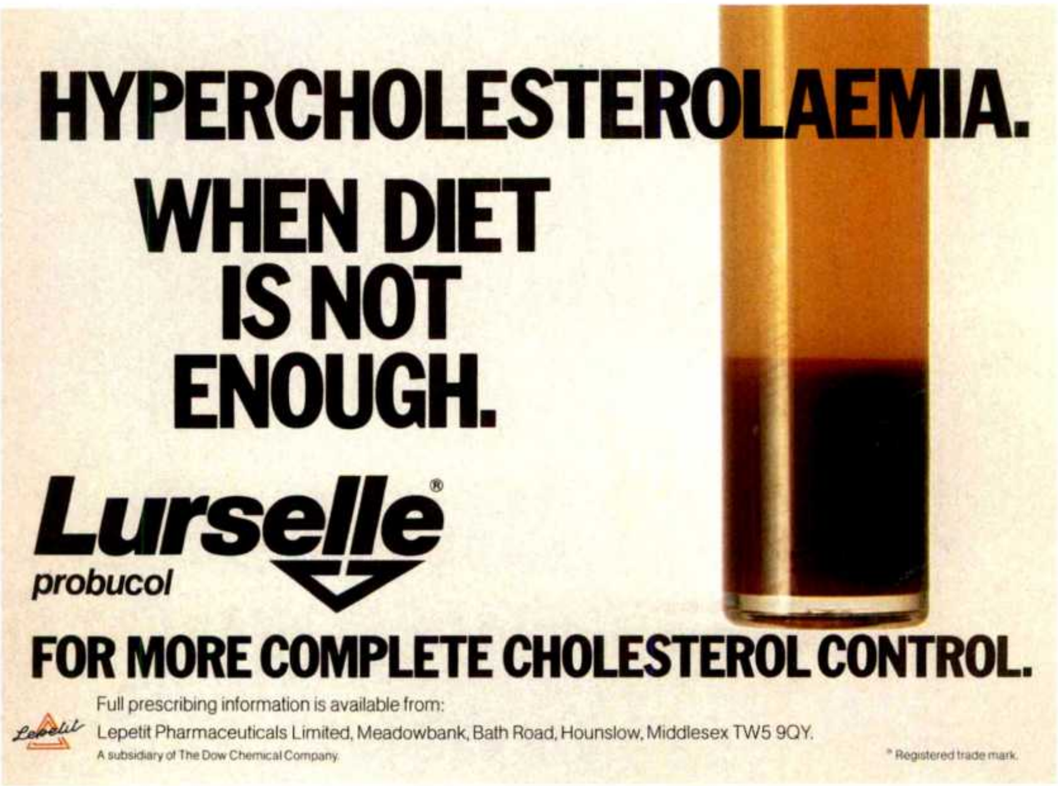

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Editorial

Br Heart J 1982; 47: 409–10

Carotid sinus syncope

A LEATHAM

From St. George's and The National Heart Hospitals, London

Every physician knows about Soma Weiss's Boston tram-driver who repeatedly blacked out on a corner from stimulation of the carotid sinus by his wing collar.[1] Further cases of so-called carotid sinus syncope have only rarely been reported. It is therefore surprising to see that Morley and his colleagues[2] describe 70 patients with carotid sinus syncope who have been treated by artificial pacing over a period of four years. This raises the problem of the definition of carotid sinus syncope. Reflex slowing of sinoatrial rate from carotid sinus massage is an almost universal finding and is perhaps more pronounced in older subjects and certainly is particularly noticeable, as one would expect, in patients with disease of the conducting tissue. Presumably Morley *et al.* are raising the interesting idea that the slowing in their cases is the result of a primary abnormality of the carotid sinus, but others would localise the primary abnormality to the conducting tissue, and in patients with sinus bradycardia and sinus pauses (but no evidence of atrioventricular conduction problems) would regard the primary diagnosis as that of sinoatrial disease. This is now known to be a very frequent abnormality and is indeed sometimes hard to differentiate from normal subjects with strong vagal tone unless they have severe symptoms or attacks of atrial fibrillation or flutter.

How then do Morley *et al.* differentiate sinoatrial disease from so-called carotid sinus syncope? In the first place they recognise that over half their patients had positive evidence of sinoatrial disease based on the presence of paroxysmal atrial fibrillation and a prolonged sinoatrial node recovery time, though the latter is of doubtful validity.[3] But they go on to state that "none of the patients had overt sick sinus syndrome on resting or 24 hour electrocardiogram". This seems a remarkable statement when one commonly sees patients with episodes of extreme bradycardia separated by weeks or months of normality.

Thus a strong case can be made for stating that most, if not all, of the patients described by Morley *et al.* simply had sinoatrial disease. The question then arises, knowing the benign course of this disease unlike atrioventricular conduction disorders, whether too many cases of this sort are being paced, and one strongly suspects that this is so particularly in the United States where 40% of all cases paced are paced primarily for sinoatrial disease, according to the World Survey of Cardiac Pacing in 1978.

In this country patients and physicians are more stoical about minor dizzy turns, particularly when months, or even years, go by without recurrence. It is, however, important to avoid drugs since some of these patients also have tachyarrhythmias (brady-tachy syndrome) which will be exacerbated by adrenergic therapy (they are also liable to thromboembolism and may require anticoagulants[4]). In the few whose symptomatology is sufficiently severe to require pacing, suppressant drugs can then be given safely. In "early cases" on a pacemaker when the patient is in sinus rhythm with a reasonable rate most of the time, the occasional onset of bradycardia, stimulating demand ventricular pacing is often noticed by the patient because of a slight fall in blood pressure, with loss of appropriate presystolic atrial contraction, and so it is not surprising that some of Morley's cases continue to have symptoms from the so-called "pacemaker effect". Whether Morley *et al.* are correct in thinking that their patients have an additional problem described as a vasodepressor response indicating an abnormal fall of blood pressure after carotid sinus massage when they only had 11 control subjects remains to be decided. Atrial pacing was used in eight of their cases, but had to be discontinued, in some because of coincidental atrioventricular block and in others because of atrial arrhythmia, both problems being expected in patients with sinoatrial disease. It is interesting to read that of the 16 patients with persistent symptoms despite advanced pacing systems, 12 had adequate bradycardia control. It is unlikely that they were suffering from vasomotor syncope from carotid sinus pressure from winged collars, and maybe their symptoms had another cause.

Further work is required to decide whether primary carotid sinus syncope is other than an extremely rare medical curiosity. In any case the estimate of 35 new patients per million per year of "carotid sinus syndrome" in the Worthing area compared with 82 new patients with atrioventricular block and sick sinus syndrome must be an exaggeration. In the meantime carotid sinus stimulation may be regarded as a means of unmasking conduction disease, though the subject is made difficult by the enormous range of physiological variation. Serious thought should also be given to whether pacing is being too frequently used for patients with sinoatrial disease. Furthermore it seems that there is seldom justification for the use of expensive sequential atrioventricular systems, particularly when most of these patients have unstable electrical activity in the atria, though modern techniques may, at least in part, overcome this problem in the future.[5]

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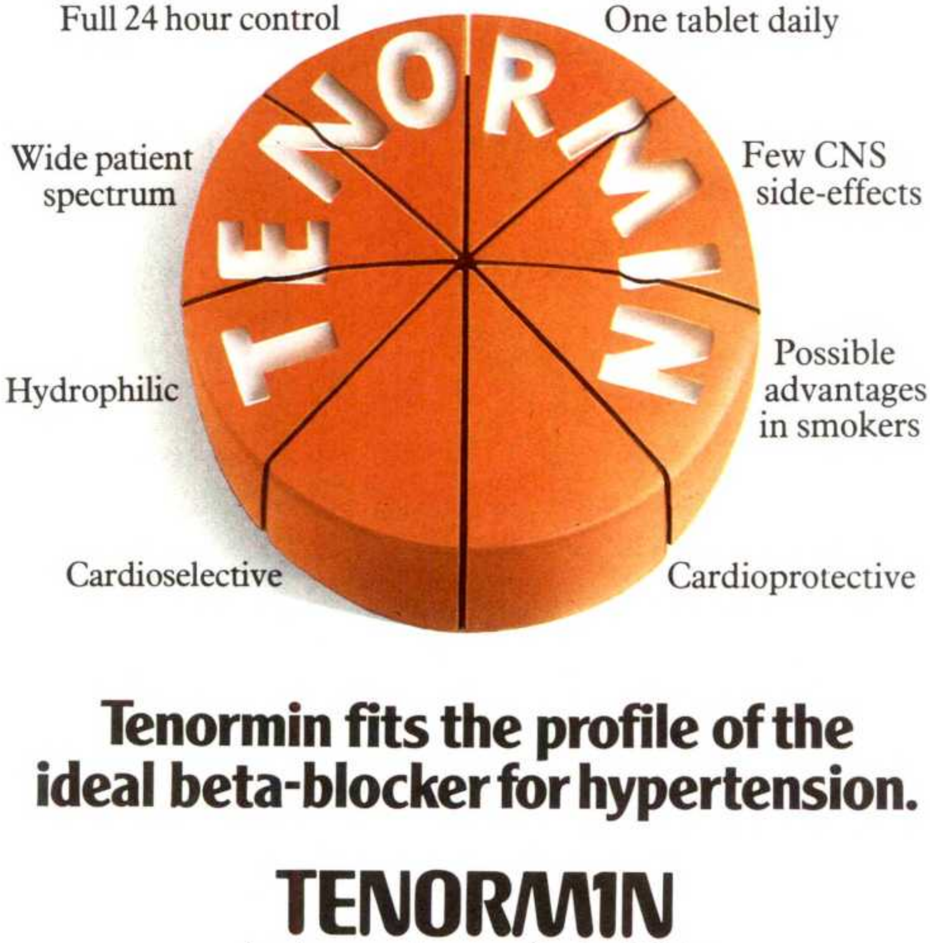

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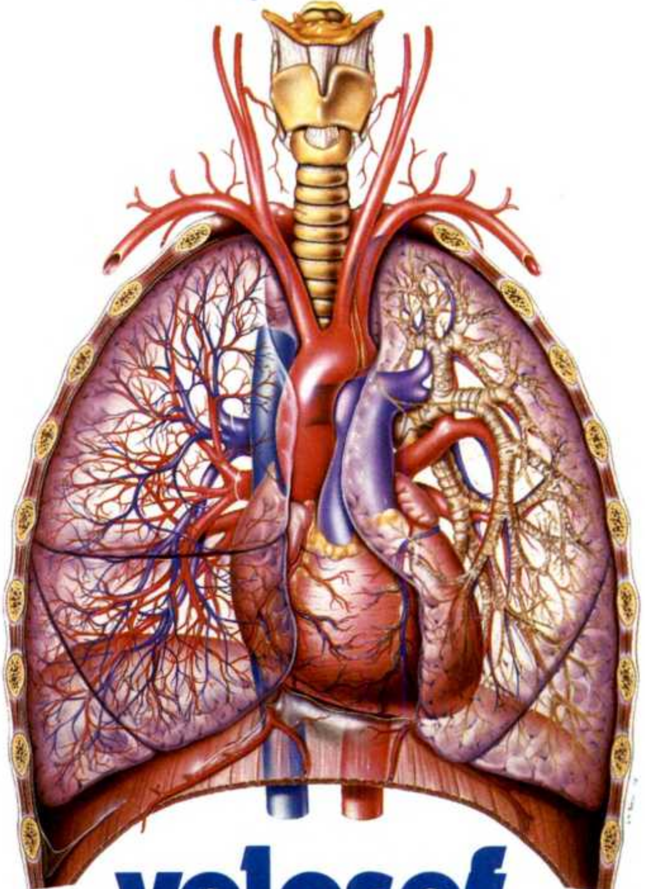

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Br Heart J 1982; 47: 411–8

Carotid sinus syncope treated by pacing

Analysis of persistent symptoms and role of atrioventricular sequential pacing

C A MORLEY,* E J PERRINS, P GRANT, S L CHAN, D J McBRIEN, R SUTTON

From Westminster Hospital, London; and Worthing Hospital, Sussex

SUMMARY Seventy patients have been paced for carotid sinus syndrome over four years. Twelve patients had persistent symptoms despite adequate ventricular pacing. Patients with persistent symptoms were found to have a significant vasodepressor response, a significant hypotensive response to ventricular pacing (pacemaker effect), and a severe hypotensive response to carotid sinus massage with introduction of ventricular pacing, which reproduced symptoms in all patients.

A group of 14 asymptomatic paced carotid sinus patients was found to have a significantly lower vasodepressor response, pacemaker effect, and combined vasodepressor response plus pacemaker effect than the group with persistent symptoms.

Atrioventricular sequential pacing was shown to eliminate the hypotensive effect of ventricular pacing and is considered to be the treatment of choice for patients with carotid sinus syndrome who have both cardioinhibitory and significant vasodepressor responses.

There has been controversy concerning the need to treat patients with a hypersensitive carotid sinus reflex since this was first recognised as a cause of syncope in man.[1] There is, however, evidence that syncopal patients with a hypersensitive carotid sinus reflex will continue to suffer disabling symptoms unless treated.[2]

Pacing is now accepted as the treatment of first choice for syncopal patients with a pure or predominant cardioinhibitory response to carotid sinus massage.[2–4] Indeed, a total of 159 patients paced for carotid sinus syndrome were reported from four cardiac centres at a recent minisymposium on carotid sinus syndrome,[5–9] with very satisfactory results.

A predominant cardioinhibitory response to carotid sinus massage is found in up to 80% of patients with carotid sinus syndrome.[10] A pure vasodepressor response is rare, occurring in 5 to 10% of cases,[11 12] but a mixed vasodepressor and cardioinhibitory response may not be uncommon.[10] Patients with such a mixed type of response pose a therapeutic problem as ventricular pacing does not correct their vasodepressor response and symptoms may persist. Recurrence of symptoms after ventricular demand pacing for carotid sinus syndrome has been previously reported[2 13 14] and has been attributed to the vasodepressor response.[13 15] Hypotension occurring with the onset of ventricular pacing (pacemaker effect) has not been previously reported as a cause of persistent symptoms, either alone, or in combination with the vasodepressor response in paced carotid sinus syndrome patients. This paper presents a sufficiently large series of patients paced for carotid sinus syndrome to allow analysis of persistent symptoms.

Patients and methods

Seventy patients with a primary diagnosis of carotid sinus syndrome were paced over a four year period. Fifty patients were men and 20 were women, and their mean age was 68 years. Sixty-one patients presented with syncope, with a mean of eight syncopal episodes per patient. The remaining nine patients had severe recurrent dizziness. The mean duration of symptoms before pacing was 20 months. One or more episodes of significant injury caused by syncope were experienced by 24% of the patients.

Carotid sinus massage was performed by standard technique[16] for six seconds, using pressure insufficient to occlude the ipsilateral temporal arterial pulse. A hypersensitive response was defined as asystole (62 patients) or complete atrioventricular block

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(eight patients) exceeding three seconds. Carotid sinus massage was positive on the right side in 52% of cases, on the left side in 15%, and on both sides in 33% of patients.

All patients with significant spontaneous symptoms and a hypersensitive carotid sinus reflex were investigated with an electrophysiological study to record the His bundle electrocardiogram, measure the sinus node recovery time, observe the presence or absence of retrograde atrioventricular conduction, and demonstrate the benefit of temporary pacing during carotid sinus massage. The electrophysiological study and resting electrocardiographic findings are summarised in Table 1.

The criteria for pacing patients with a hypersensitive carotid sinus reflex were reproduction of symptomatic asystole exceeding three seconds and abolition of symptoms by temporary ventricular pacing during repeated carotid sinus massage. The effectiveness of carotid sinus massage was ensured in most patients by observing atrial asystole during temporary ventricular pacing (Fig. 1).

ANALYSIS OF PERSISTENT SYMPTOMS

Patients have been followed up for a mean duration of 18 months since first pacemaker implant. Three groups of patients have been studied using intra-arterial pressure monitoring.

Group 1: 12 patients with carotid sinus syndrome who had persistent symptoms despite ventricular pacing giving adequate bradycardia control.

Group 2: 14 patients with carotid sinus syndrome who were asymptomatic after pacing.

Group 3: 11 patients who did not suffer from the carotid sinus syndrome. These patients had been investigated for syncope or dizziness, but had no evidence of carotid sinus syndrome.

Measurements of either brachial or radial intra-arterial pressure were taken using 40° head up tilt to control the effect of posture on arterial pressure. Phasic arterial pressure and the electrocardiogram were recorded simultaneously using a Statham P23 ID transducer and Hewlett Packard recorder. The mid-axilla was used as the zero reference point. The following variables were investigated to determine the role of hypotension in causing persistent symptoms in patients paced for carotid sinus syndrome.

VASODEPRESSOR RESPONSE

Vasodepressor response was measured as the greatest fall in systolic arterial pressure after carotid sinus massage during atrioventricular sequential (DVI)* pacing (Fig. 2). Nine patients had permanent DVI pacing. Patients without DVI units were investigated either with temporary DVI pacing (21 patients) or after atropine to eliminate the cardioinhibitory response to carotid sinus massage (seven patients) so that they remained in sinus rhythm during carotid sinus massage, with minimal bradycardia.

PACEMAKER EFFECT

The pacemaker effect was measured as the maximum fall in systolic arterial pressure after the introduction of ventricular demand pacing from sinus rhythm (Fig. 3). This was achieved by externally programming the pacemaker from a rate less than sinus rate to a rate just sufficient to overdrive sinus rhythm. Patients with DVI units were reprogrammed to ventricular pacing mode. The effect of the introduction of DVI pacing on arterial pressure (Fig. 2) was similarly measured in the 30 patients studied with either permanent or temporary DVI pacing.

COMBINED PACEMAKER EFFECT AND VASODEPRESSOR RESPONSE

Pacemaker effect plus vasodepressor response was measured as the maximum fall in systolic arterial pressure after simultaneous carotid sinus massage and introduction of ventricular pacing (Fig. 2). This was achieved by programming to a demand rate just below sinus rate before carotid sinus massage. The carotid sinus cardioinhibitory reflex results in bradycardia and onset of ventricular pacing.

Table 1 *Resting electrocardiogram and electrophysiological study results*

Electrocardiogram (70 patients)		*Electrophysiological study (67 patients)*	
Normal	49%	Normal	34%
Ischaemia	14%	Sinus node recovery time prolonged	39%
Left anterior hemiblock	12%	Paroxysmal atrial fibrillation	16%
Left bundle-branch block	9%	HV≥ 60 ms His bundle electrocardiogram	20%
First degree heart block	4%	AH≥110 ms	5%
Left ventricular hypertrophy	4%	Retrograde atrioventricular conduction present	*80%
Atrial fibrillation	4%		
Other minor electrocardiographic abnormalities	12%	*(mean stimulus to retrograde "p" wave interval = 179 ms)	

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*In this three-letter code the first letter indicates the chamber paced; the second, the chamber sensed; and the third, the mode of response (I=inhibited; T=triggered; A=atrium; V=ventricle; D=both chambers; O=neither chamber) (Parsonnet V, Furman S, Smyth NPD. Report of the Intersociety Commission for Heart Disease Resources: implantable cardiac pacemakers—status report and resource guideline. *Am J Cardiol* 1974; 34: 487–500).

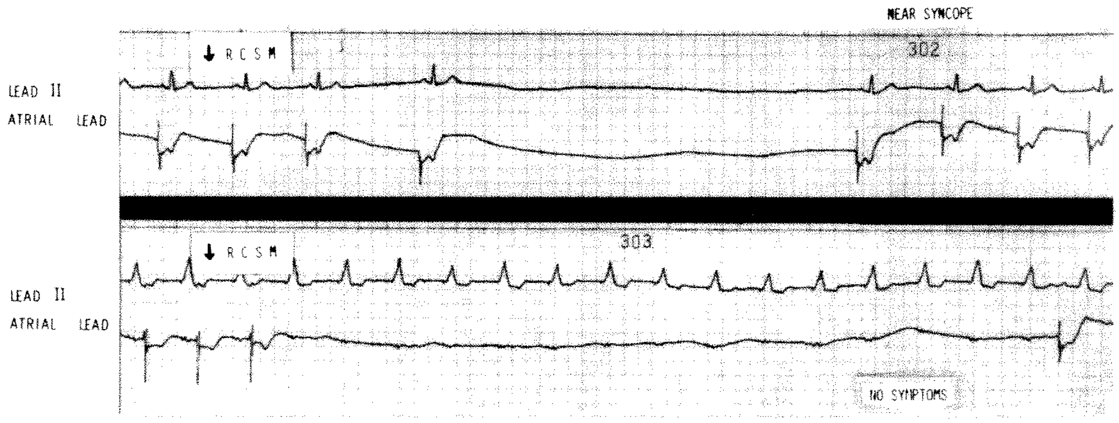

Fig. 1 *Criteria for diagnosing carotid sinus syndrome at electrophysiological study. Simultaneous recording of scalar electrocardiogram lead I with endocardial recording from high right atrium. RCSM, right carotid sinus massage.*

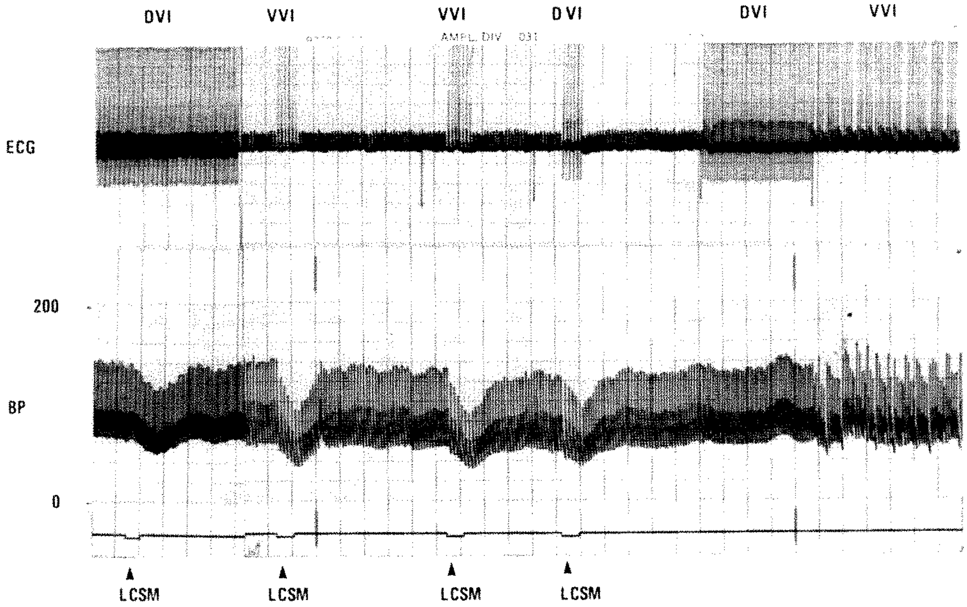

Fig. 2 *Arterial pressure recordings during sinus rhythm, ventricular pacing, atrioventricular sequential pacing, and carotid sinus massage. Scalar electrocardiogram lead I (upper panel) recorded simultaneously with intra-arterial pressure (brachial or radial) in the lower panel. Paper speed 1 mm per second. DVI, atrioventricular sequential pacing; VVI, ventricular pacing; ECG, electrocardiogram; BP, arterial pressure; LCSM, left carotid sinus massage.*

INCIDENCE OF CAROTID SINUS SYNDROME

An estimate of the incidence of carotid sinus syndrome was calculated from the figures for referral from a single district general hospital (Worthing Hospital, West Sussex). All patients presenting to Worthing Hospital with syncope of possible cardiac origin are referred to Westminster Hospital for consideration of pacing. The calculation was made in a similar way to that in which Johansson first estimated the incidence of complete heart block in the population.[17] The catchment population of Worthing Hospital was 235 000 people in 1979. Thirty-three patients have

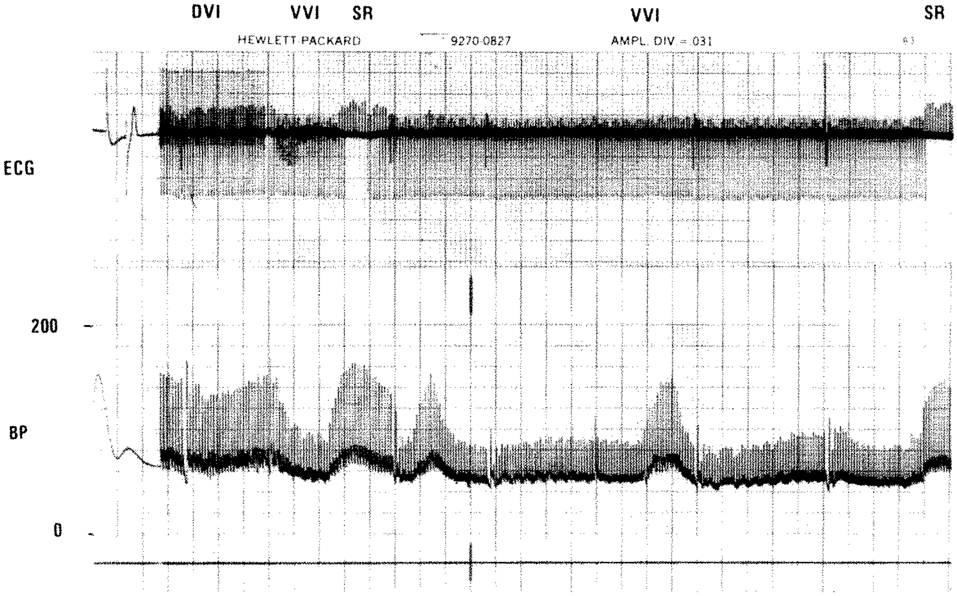

Fig. 3 *Demonstration of pacemaker effect. The hypotensive effect of VVI pacing is sustained, but may intermittently recover, as shown above, because of atrioventricular dissociation and periodic atrial contraction during diastole. Scalar electrocardiogram lead II (upper panel) recorded simultaneously with intra-arterial pressure (lower panel). 1 mm per second paper speed.*

been referred over four years (1977 to 1981) with a primary diagnosis of carotid sinus syndrome and 77 patients with either atrioventricular block or sick sinus syndrome. From these figures the estimated incidence of carotid sinus syndrome for the Worthing area was 35 new patients per million population per year and for atrioventricular block plus sick sinus syndrome 82 new patients per million population per year. This compares with the United Kingdom figure (1978) for average new pacemaker implants of 75 new patients per million per year.[18]

Results

The initial and final pacing modes and the incidence of persistent symptoms in the 70 patients with carotid sinus syndrome are shown in Table 2.

Complete relief of symptoms before unit change was achieved in 77% of patients (85% of patients with VVI pacing, all patients with DVI/DDD pacing, and none of the eight patients with atrial pacing). After conversion of pacing symptoms (see Table 2), complete relief of symptoms was achieved in 89% of patients. There have been only four deaths: three in the asymptomatic group (two deaths from carcinoma and one from cerebrovascular accident) and one death in the group with persistent symptoms which was sudden and unexplained.

PERSISTENT SYMPTOMS

Initially 16 patients had persistent symptoms. Eight of these patients had atrial (AAI) pacemakers, and eight had ventricular (VVI) pacemakers. All eight atrially paced patients had symptomatic atrioventricular block during carotid sinus massage (Fig. 4). Their symptoms were therefore attributed to lack of adequate control of bradycardia, and these patients were electively converted to either a ventricular or dual chamber pacing system (VVI or DVI/DDD).

Four of these patients are now asymptomatic with DVI or DDD pacemakers, but four had persistent symptoms despite conversion to VVI (two patients), DVI (one patient), and DDD (one patient). Thus 12 patients were left with persistent symptoms despite adequate control of bradycardia (10 VVI, one DVI, one DDD).

The results of the arterial pressure studies in these 12 patients, the asymptomatic carotid sinus syndrome group, and the group without carotid sinus syndrome are shown in Table 3 and Fig. 5. The vasodepressor response was significantly greater in the patients with carotid sinus syndrome (groups 1 and 2) than in the controls (group 3), with $p<0{\cdot}05$. The vasodepressor response was also significantly greater ($p<0{\cdot}001$) in the group with persistent symptoms (group 1) than in the asymptomatic group with carotid sinus syndrome (group 2). The combined hypotensive effect of vaso-

Table 2 *Symptoms according to initial and final pacing mode*

Pacing mode	*Initial pacing mode*	*Persistent symptoms*	*Final pacing mode*	*Persistent symptoms*
VVI	55*	8	54	6
AAI	8†	8	0	—
DVI	6	0	13	1
DDD	1	0	3	1

*Four VVI converted to DVI.
†Five AAI converted to DDD/DVI; three AAI converted to VVI.

depressor response and pacemaker effect was greatest in the group with persistent symptoms (group 1) $p<0{\cdot}01$. The isolated pacemaker effect was also greatest in this group, $p<0{\cdot}05$. No significant hypotension was demonstrated with the onset of atrioventricular sequential pacing.

Table 4 shows that the three groups were comparable for age, incidence of ischaemic heart disease, and hypertension. Women predominated in the group without carotid sinus syndrome and evidence of sinoatrial disease was more common in patients with the carotid sinus syndrome.

Discussion

There has been an unexpectedly high incidence of carotid sinus syndrome. The criteria used for diagnosing carotid sinus syndrome were stringent. Only patients with disabling symptoms or definite syncope were paced. Hypersensitive carotid sinus reflex was diagnosed at the bedside and subsequently confirmed at electrophysiological study, which allowed assessment of other cardiac conduction defects and confirmation that symptoms precipitated by carotid sinus massage could be abolished by temporary pacing (Fig. 1). There was a high incidence (55%) of electrophysiological evidence of sinoatrial disease (either prolonged sinus node recovery time or paroxysmal atrial fibrillation precipitated by atrial pacing). This association has been noted by others.[19] None of the patients had overt sick sinus syndrome on resting or 24 hour electrocardiogram. All patients were therefore considered to have a primary diagnosis of carotid sinus syndrome.

Eight patients early in this series were selected for atrial pacing on the grounds of haemodynamic benefit of atrial pacing shown at catheterisation (cardiac output and mean aortic pressure recordings) and control of bradycardia without atrioventricular block at electrophysiological study. Atrial pacing, however, is clearly contraindicated in view of the appearance of recurrent symptoms in all atrially paced patients with carotid sinus syndrome and the demonstration of symptomatic atrioventricular block with carotid sinus massage at follow up.

Four of the atrially paced patients continued to have symptoms after pacemaker conversion, two to VVI, one to DVI and one to DDD pacing. Of these four patients, the two with VVI pacing were shown to have a combination of vasodepressor response plus pacemaker effect sufficient to explain their symptoms and the DVI and DDD patients both had severe vasodepressor responses.

Ventricular demand (VVI) pacing was successful in 85% of patients who were initially selected for VVI pacing. These results are superior to results of irradiation[10,20] or carotid sinus denervation.[21-23] The 12 patients with persistent symptoms were all shown to have a significant vasodepressor response and consid-

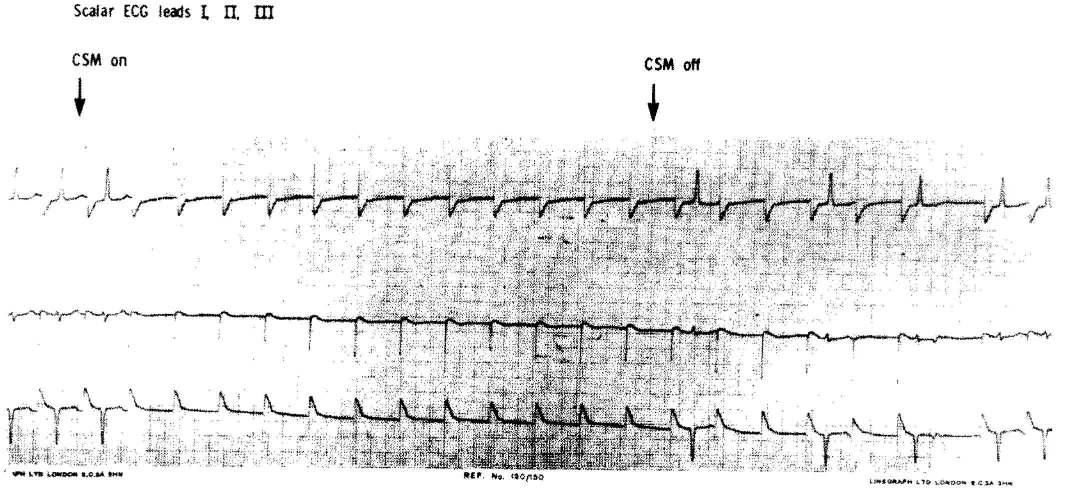

Fig. 4 *Carotid sinus massage (CSM) preventing normal atrioventricular conduction in atrial pacing.*

Table 3 *Arterial line results*

	No. of patients	*Symptoms*	*↓SBP mmHg*		*p value**
(1) Vasodepressor response (VDR)					
CSS symptomatic	12	4	51·8±15	<0·001	<0·001
CSS non-symptomatic	14	Nil	28·9±14	<0·05	
Non CSS	11	Nil	14·4±19		
(2) Pacemaker effect (PME) SR→VVI					
CSS symptomatic	11†	Nil	52·2±10	<0·05	<0·01
CSS non-symptomatic	14	Nil	42 ±12	NS	
Non CSS	11	Nil	35·4±14		
(3) VDR+PME					
CSS symptomatic	11†	11	76·1±19		<0·01
CSS non-symptomatic	14	4	50 ±16		
(4) PME SR→DVI					
All groups	30	Nil	6 ± 9		

*Student's t test for unpaired data.
†One symptomatic CSS patient was in chronic atrial fibrillation and therefore PME and VDR+PME could not be measured.

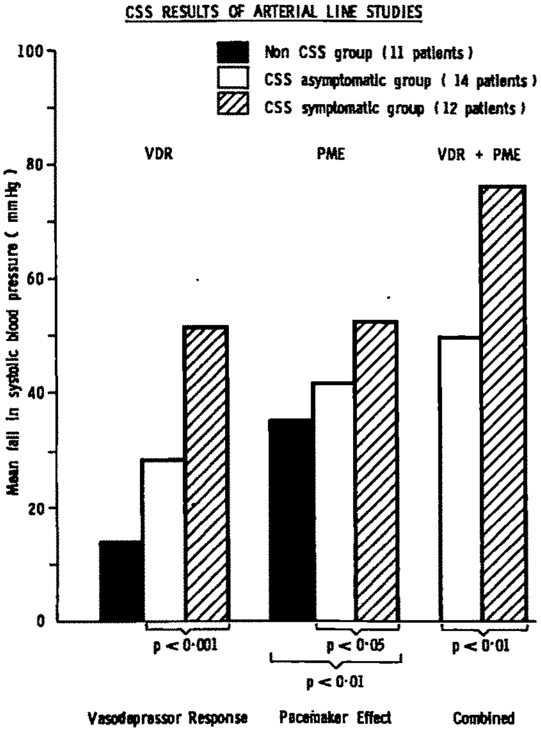

Fig. 5 *Histogram showing results of arterial pressure study. CSS, carotid sinus syndrome.*

Table 4 *Comparison of groups 1, 2, and 3 of arterial pressure study*

	Group 1 CSS symptomatic	*Group 2 CSS non-symptomatic*	*Group 3 Non CSS*
Number	12	14	11
Male	7	10	4
Female	5	4	7
Mean age (y)	69	67	65
Ischaemic heart disease	3	3	4
Hypertension	2	2	1
Cerebrovascular disease	2	0	0
Sick sinus syndrome	6	7	2
Intermittent atrioventricular block	0	0	2

erable hypotension when the effects of vasodepressor response and onset of ventricular pacing were combined. Symptoms could be elicited in only four patients by vasodepressor response alone (one patient was in chronic atrial fibrillation) but in all patients by vasodepressor response plus pacemaker effect. No patient was symptomatic with onset of ventricular pacing alone, even when retrograde ventriculoatrial conduction was observed, and therefore the pacemaker effect is unlikely to be the only cause of their symptoms.

The pacemaker effect was found to be greatest in the group with persistent symptoms of carotid sinus syndrome, but not significantly different between the asymptomatic group with carotid sinus syndrome and the group without carotid sinus syndrome. The three groups were comparable for age and incidence of hypertension and ischaemic heart disease. It is therefore unlikely that the difference in pacemaker effect was caused by a significant difference in cardiac function. Alicandri *et. al.*[24] have proposed that the hypotension that occurs during ventricular pacing is not solely the result of the haemodynamic consequences of atrioventricular dissociation but that there may be an atrial stretch reflex in man (as shown in cats[25]) which is activated by the high atrial pressures. These occur when the atria contract against closed atrioventricular valves. The response to this reflex might be expected to be greater in patients with a vasodepressor response to carotid sinus massage as presumably they have a hypersensitive vasomotor centre.

Atrioventricular pacing has been shown to abolish the pacemaker effect and is therefore likely to be helpful in the persistent symptoms group. Four of the patients with ventricular pacemakers have been converted to DVI pacing with improvement, but follow up is too short to make further comment. The remaining six symptomatic VVI paced patients have been considered for conversion to DVI pacing. One patient is excluded because of chronic atrial fibrillation, one patient has refused conversion, and four patients have only mild or infrequent symptoms and are being followed up closely.

Four patients (two VVI, one DVI, one DDD) were shown to have a vasodepressor response sufficient to cause symptoms without additional pacemaker effect and at present there is no satisfactory treatment for these patients, but DVI pacing may, however, reduce the severity of their symptoms by eliminating the carotid sinus cardioinhibitory response and pacemaker effect. Arterial pressure study before pacing patients with carotid sinus syndrome is helpful in selecting the most appropriate mode of pacing. Patients with a vasodepressor response or combinations of vasodepressor response plus pacemaker effect sufficient to reproduce symptoms, in addition to cardioinhibitory response, should be selected for DVI pacing.

In this series 89% of patients have been rendered asymptomatic with appropriate choice of pacing system. Forty-eight patients (68%) are asymptomatic with VVI pacing, and 14 with DVI/DDD pacing. A further four patients symptomatic with VVI pacing would almost certainly benefit from conversion to DVI pacing which is therefore considered the most appropriate mode of pacing in 18 patients (26%). Only four patients (6%) are likely to remain symptomatic, regardless of pacing mode, in view of severe vasodepressor response.

The hypersensitive carotid sinus syndrome is thus more common than previously recognised and cardiac pacing is a highly effective treatment provided the correct mode is selected.

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Anatomical-embryological correlates in atrioventricular septal defect

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SUMMARY Recent embryological studies have supported the consideration that the ventricular septum is multifocal in origin. These data have also provided excellent correlation of the morphology of malformed hearts with their embryology. In particular, atrioventricular septal defect correlates accurately with these observations on ventricular septation. Many of the names given to atrioventricular septal defect (for example ostium primum, persistent atrioventricular canal, endocardial cushion defect) indicate attempts at correlating the anatomy with embryology. None of these has been very convincing.

In the light of this uncertainty, this review considers briefly the anatomy of the malformation and its ontogeny, and presents a hypothesis of the development of atrioventricular septal defect.

Although there is almost always a communication above the atrioventricular valves, the malformation lies in the ventricular, not the atrial septum. Hearts with inlet septal defect without interatrial communication represent one end of the spectrum of anomalies, and those with common atrioventricular orifice, in which Fallot's tetralogy or single outlet heart may be associated, mark the other end. The outflow tract malformations are not randomly associated, but are points in a huge range of cardiac malformations.

Atrioventricular septal defect is a cardiac malformation characterised externally by an abnormally short posterior (diaphragmatic) ventricular surface.[1] Internally there is a gap between the concave inferior rim of the atrial septum (which is usually well developed) and the atrioventricular valves. There may be a common atrioventricular valve, usually with five or six leaflets of which the two major ones, anterior and posterior, bridge the ventricular septum.[2] Often there are two valves, each with three leaflets[3] (Fig. 1a, b). The left component has an abnormally orientated anterior leaflet which is separated medially from the septal or posterior leaflet by an unsupported division which is usually called a cleft. Between the anterior and septal leaflets, at the obtuse margin, is the lateral leaflet (Fig. 1b). When there is a bridging leaflet between either the anterior and lateral, or posterior and lateral leaflets, it produces an accessory orifice, and is common in atrioventricular septal defect.[1 3] The leaflets themselves are often poorly developed and may have a verrucous appearance.

The short external diaphragmatic surface of the ventricular mass is reflected internally by a pronounced disproportion between the inlet and outlet lengths of the left ventricle. In normal hearts these two measurements are essentially the same.[1] In atrioventricular septal defect the outflow tract of the left ventricle is long and narrow compared with a normal heart (Fig. 2a, b) and the left anterior leaflet inserts immediately behind and beneath the aortic valve so that the latter is displaced. (Whether the valve is really displaced has been debated at length[4–6] but the appearance is that of displacement.) It has lost its wedged position between the atrioventricular valves and the ventricular septum.[7 8] Sometimes aortic outflow tract obstruction occurs, and muscular obstruction may be further aggravated by hypoplasia of the aortic valve.[9]

Pulmonary outflow tract obstruction is especially associated with a common valve with bridging leaflets[2] and may be the result of the infundibular septal derangement characteristic of Fallot's tetral-

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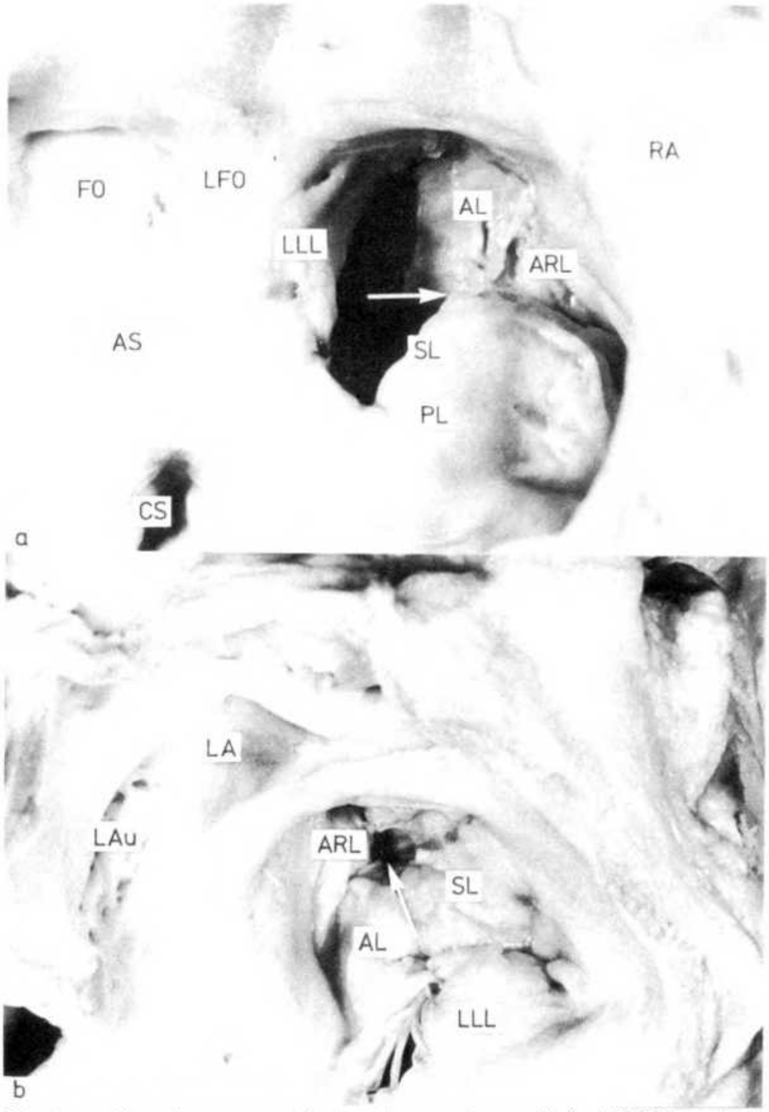

Fig. 1 *(a) The atrioventricular valves in atrioventricular septal defect (AVSD) seen from the right atrium (RA). The atrial septum (AS) is intact and its concave rim forms the "roof" of the AVSD. The valve leaflets are attached at the same level to the summit of the muscular septum, but the anterior (AL) and posterior (PL), or septal (SL) bridging leaflets are separated by the "cleft" (arrowed). LLL, lateral left leaflet; ARL, anterior right leaflet; CS, coronary sinus; FO, fossa ovalis; LFO, limbus fossa ovalis. (b) Same heart, left atrial (LA) view. The left valve does not resemble a normal mitral valve. It has three leaflets, anterior, septal or posterior, and lateral. The abnormally orientated anterior leaflet is separated by the cleft (arrowed) from the septal or posterior bridging leaflet. LAu, left auricle. Other abbreviations as in Fig. 1(a).*

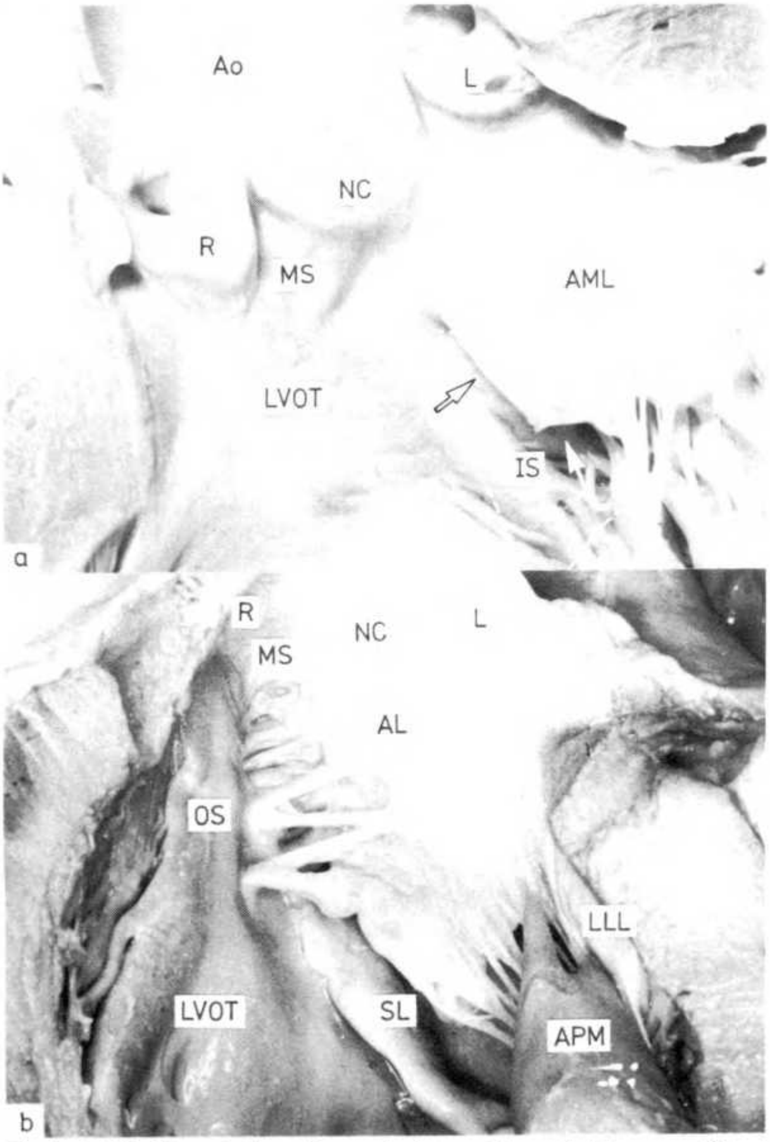

Fig. 2 *(a) The left ventricular outflow tract in the normal heart. The inlet septum (IS) and its atrioventricular component, indicated by the dotted line, give "depth" to the outflow tract. The atrioventricular septum extends from the membranous part of the septum (MS) to the crux cordis permitting a posterior recess (arrowed). The anterior mitral leaflet (AML) is normally orientated, and extends from the base of the left aortic leaflet (L) to the non-coronary leaflet (NC). Thus the aortic valve is "wedged" by the inlet septum and the mitral valve, so that it lies beside rather than anterior to the mitral valve. Ao, aorta; LVOT, left ventricular outflow tract; R, right aortic leaflet. (b) The left ventricular outflow tract in AVSD. The narrowness is partly the result of the deficiency of the inlet septum and absence of its atrioventricular component (note the septal attachment of the anterior leaflet (AL) of the left valve) and partly of attenuation of the outlet septum (OS). The loss of the normal "wedge" position of the aortic valve is shown by the position of the anterior leaflet which extends from the left aortic leaflet to the commissure between non-coronary and right (R) leaflets. The membranous part of the septum is small, but intact. APM, anterior papillary muscle group. Other abbreviations as in Fig. 1.*

ogy. Double outlet right ventricle, ventriculoarterial discordance, and single outlet heart are also sometimes represented in atrioventricular septal defect.[10–12]

The atrial septum is usually well developed in atrioventricular septal defect; the anticipated normal anatomical elements are represented and atrial septation is often complete, especially in those with "partial" or "transitional" defects (Fig. 1a and b). Patency of the foramen ovale, however, occurs with some frequency, as in the normal heart, and secundum atrial septal defects are common. In view of the frequent finding of a normal atrial septum it is, perhaps, surprising that so many investigators have concluded that the development of this structure is at fault in atrioventricular septal defect. The defect itself is the gap between the inferior rim of the atrial septum and the atrioventricular valves. The vertical dimension of this defect is approximately the same as the disproportion between the inlet and outlet length of the ventricular septum measured in the left ventricle (Table 1). These data strongly suggest that the anomaly concerns the inlet ventricular septum rather than the atrial septum.

The foregoing paragraphs are not intended to be an exhaustive description of atrioventricular septal defect, but to indicate the spectrum which can accurately be correlated with the ontogeny of the ventricles and the ventricular septum.

Historical background

Atrioventricular septal defect was first described by Peacock[13] who considered imperfect ventricular septation to be involved in the anomaly. In view of recent embryological findings, Peacock's view is of some interest, as many of those who followed him considered only defective or arrested septation to be responsible. The history of the terminology and the gross classification are summarised in Table 2.

Table 2 *Nomenclature and morphology in atrioventricular septal defect*

Peacock[13] 1846	Imperfection of atrial and ventricular septa
Rokitansky[14] 1875	Atrioventricular canal defect Partial −VSD Complete +VSD
Watkins and Gross[16] 1955	Endocardial cushion defect Ostium primum ASD
Wakai and Edwards[17] 1956	Persistent common AV canal Partial separate atrioventricular valves Transitional almost separate atrioventricular valves ±small VSD Complete common atrioventricular valve
Bedford *et al.*[18] 1957	Atrioventricular defect
Brandt *et al.*[19] 1972	Endocardial cushion defect Partial −VSD Complete +VSD
Piccoli *et al.*[5,6] 1979	Partial separate atrioventricular valves Complete common atrioventricular valve

ASD, atrial septal defect; VSD, ventricular septal defect.

With respect to "partial" and "complete" defects, most authors have adhered to Rokitansky's[14] division between those with interatrial communication only (partial) and those who had an interventricular defect as well.[15–19] More recently, however, the two terms have been used to distinguish between separated atrioventricular (partial), and common orifice (complete),[5–6] but this distinction has not gained general currency, especially in surgical practice.[2,3] Wakai and Edwards[20] described a third type of atrioventricular septal defect which they termed "transitional" or "intermediate". These hearts had two "cleft" atrioventricular valves and a "narrow bridge of valvular tissue in the midline (which) joins the anterior half of each of the two cleft atrioventricular valvular leaflets with their respective posterior halves just above the ventricular septum". In four of the six hearts which they described there was a small interventricular communication as well. Thus the "transi-

Table 1 *Measurements of inlet and outlet septa in left ventricle, and of vertical dimension of defect in 10 hearts with atrioventricular septal defect, situs solitus, and concordant ventriculoarterial connections*

No.	*AV valves*	*Septal length (mm)*		*Inlet outlet difference (mm)*	*Vertical dimension of defect (mm)*
		Inlet	*Outlet*		
1	Common	28	48	20	20
2	Separate	30	38	8	10
3	Common	29	41	12	16
4	Almost separate	36	55	19	21
5	Common	36	47	11	12
6	Separate	35	62	27	28
7	Separate	40	54	14	16
8	Common	25	40	15	16
9	Separate	40	65	25	25
10	Common	31	51	20	22

Note: The discrepancy is much the same as the vertical dimension of the defect, and the figures accord with those given by Goor *et al.*,[1] that is that there is about 30% difference between the two. Thus the inlet septum represents about one third of the septal mass.

tional" group are like those with "partial" atrioventricular septal defect because they have two separated valves, but they also resemble "complete" atrioventricular septal defect because they have an interventricular communication.

With respect to the interventricular communication, the authors considered it to represent a deficiency of the membranous part of the septum.[17,20] This structure, however, is usually present and intact in atrioventricular septal defect though it is abnormally located[5,6] (Fig. 2b).

(1) VENTRICULAR SEPTUM

In order to correlate the features described, it is necessary to describe the inlet ventricular septum and its atrioventricular component and to review recent embryological studies of ventricular septation.

The inlet ventricular septum is that part of the septum which separates the inlet portions of the left and right ventricles. It is triangular in shape (Fig. 3) and is identified in both ventricles as the smooth septum posterior and superior to the papillary muscles. On the right ventricular surface its boundaries are the tricuspid annulus and the chordal insertion of the septal leaflet of the tricuspid valve. In the left ventricle the boundaries are less well defined as the inlet septum coalesces with the trabecular septum, which extends basally to the membranous part of the ventricular septum.

The atrioventricular septum: the leaflets of both atrioventricular valves are attached to the inlet ventricular septum; because the tricuspid leaflets are attached slightly more towards the apex than those of the mitral valve, a part of the inlet musculature interposes between the right atrium and the left ventricle. This is the muscular atrioventricular septum. It lies below and posterior to the membranous part of the septum, and is distinct from it (Fig. 2a). It extends from its points of coalescence with the trabecular and membranous septa to the crux cordis, producing a well defined posterior recess behind the anterior mitral leaflet. This recess not only gives an anteroposterior dimension to the left ventricular outflow tract but also contributes to the normal wedged position of the aortic valve between the two ventricular inlets and the atrioventricular valves.[7,8]

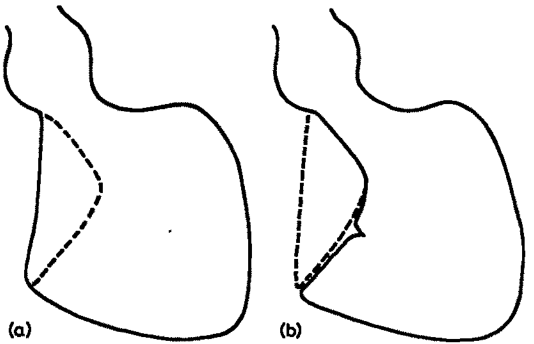

Fig. 3 *(a) Diagrammatic outline (from a left ventricular angiocardiogram) to show the position of the inlet septum. It is wedge-shaped and occupies the area between the mitral valve and the outlet septum (broken lines). (b) The same view in AVSD. The left valve (solid line), notched to indicate gap between the leaflets (the cleft), has "descended" into the left ventricle. The broken lines represent the deficient inlet septum.*

Normal cardiac septation: the ventricular septum, as its adult morphology suggests, is multifocal in origin.[21-27] Before septation has begun the inlet and outlet parts of the ventricular loop are distinguishable from one another, and both contribute to the two adult ventricles.[24] As the loop elaborates an inlet-outlet foramen becomes recognisable between the two limbs of the loop. This foramen is orientated in such a manner that subsequent septation will place its basal portion in the left ventricle and the apical part in the right ventricle. According to Wenink[27] some of the anterior leaflet of the mitral valve elaborates from endocardium from the apical part. The inlet part of the septum develops from loose trabeculations in the posterior wall of the embryonic ventricular mass, while the outlet septum develops from cushions in the outlet part and subsequent infolding of the walls of the outlet.[28]

By 33 to 34 days (7·5 mm crown-rump) trabeculations appear in the posterior ventricular wall. By 43 days (15 mm crown-rump) these have coalesced to divide the inlet portions of the ventricle. This new inlet septum is obvious at 25 mm (53 days), and by this time the process of undermining of the myocardium which will form the atrioventricular valves and their papillary muscles is under way.[26] By 28 mm this undermining is well advanced and the trabecular septomarginalis is emancipated from the septal myocardium. In the adult heart no tensor apparatus is found anterior to the trabecular septomarginalis.

The endocardial cushions, for so long considered to be precursors of the atrioventricular valves and to play a major part in both atrial and ventricular septation,[4,8] are prominent embryonic cell masses which are first distinguishable at 29 days (3·6 mm).[26] They function as valves in the embryonic heart[29,30] and have regressed by the time (53 days) the atrioventricular valves have elaborated from the ventricular myocardium. This, according to Van Gils,[30] is their primary function and they have no role in the septation of the inlets or in forming the adult atrioventricular valves.

(2) ATRIAL SEPTUM

The sequence of events which septate the atria begins fractionally later than that of the ventricles. The sep-

Table 3 *Timing of events in normal cardiac septation*

Gestational age (d)	*Crown-rump length (mm)*	*Event*
29–30	3·6	Atrioventricular canal, endocardial cushions, inlet outlet foramen
32	5	Septum primum, ostium primum, endocardial cushions
33–34	7·5	Ventriculobulbar septum, posterior trabeculations visible, right part of atrioventricular canal in direct contact with outlet of future right ventricle
36	10	Ostium primum almost obliterated: septum primum degenerates, ostium secundum formed
43	15	Posterior trabeculations form inlet septum, some begin coalescence to form atrioventricular valves
46	18	Septum secundum meets septum primum anteriorly; septum primum forms foramen ovale
53	25	Endocardial cushions rapidly regressing, myocardial undermining emancipates trabecular septomarginalis and atrioventricular valves
240	Birth	Foramen ovale (septum primum) usually closes

tum primum and endocardial cushions are evident at 32 days (5 mm) and the ostium primum is almost obliterated by 36 days (10 mm).[31] The septum primum then degenerates to permit a second pathway, the ostium secundum. At about 46 days (18 mm) the septum secundum meets the septum primum anteriorly to form a new opening—the foramen ovale. As is universally recognised, atrial septation is not completed until a short time after birth. Cardiac septation is summarised in Table 3.

Hypothetical development of atrioventricular septal defect

From the foregoing review of normal septation it is possible to hypothesise a developmental background for atrioventricular septal defect.

Although the atrioventricular valve deformities are of supreme surgical importance, in anatomical terms they are secondary to and consequent upon the malformation of the ventricular septum.

DEFECT OF INLET SEPTUM

Abnormal development of the posterior ventricular wall produces a deficiency of the posterior, inlet septum. Because the atrioventricular valves also develop from the posterior myocardium, they are automatically deformed when the posterior septum is deficient. A small degree of posterior maldevelopment might result in a modest defect below and behind the valves, usually called a "canal type defect".[32] Most "canal type defects" are in fact excavated malalignment/perimembranous defects,[5] but where there is a genuine inlet/outlet discrepancy of the left ventricle, they are true atrioventricular defects.[7] A bigger posterior septal deficit would carry the valves down into the ventricles, so the gap (defect) is between them and the floor of the atrial septum (so-called ostium primum atrial septal defect). A huge deficit, readily measured anatomically (Table 1), permits the big interventricular communication extending as far forwards as the anterior septum. The septal deficiency is large enough to leave the valves behind, so that the major leaflets of the common valve float, bridging the septal deficit. Because the anterior mitral leaflet elaborates from the outlet part of the loop, it remains high in the left ventricle, sometimes attached to the posterior rim of the outlet septum and the aortic valve (Fig. 4a, b).

ADDITIONAL ANOMALIES

Because the inlet/outlet foramen develops before the inlet septum, coincidental maldevelopment of this region would just antedate inlet septum deficiency. As the foramen is orientated before its septation, myocardial cells are carried to the basal part of the left ventricle. In normal development these contribute to the anterior mitral leaflet. The same probably occurs in atrioventricular septal defect, permitting attachment of the left valve beneath the aortic valve when the defect is small. If the deficiency of the inlet septum is large, however, then the aortic valve may lose its anchorage in the left ventricle and become a right ventricular structure. Maldevelopment of the outlet septum such as anterior deviation of the outlet (bulbar) cushions would produce infundibular obstruction such as that in Fallot's tetralogy[33] and this may be exacerbated by muscle bands and abnormal placement and development of the trabecula septomarginalis.[34]

The final morphology of atrioventricular septal defect is determined by two factors—the extent of posterior septal deficiency governs the size of the defect (and probably the valve morphology too) while the degree of maldevelopment of the ventriculo-infundibular cushions dictates the morphology of the outflow tracts.

Correlates

(1) VENTRICULAR SEPTUM IN ATRIOVENTRICULAR SEPTAL DEFECT

The anatomical hallmarks of atrioventricular septal defect are deficiency of the triangular inlet septum and absence of its atrioventricular component. Deficiency of the inlet septum is shown by the short diaphragmatic surface, which is represented internally by the concave appearance of the septal surface (Fig. 4a, b). Absence of the atrioventricular part of the inlet ventricular septum is shown by three abnor-

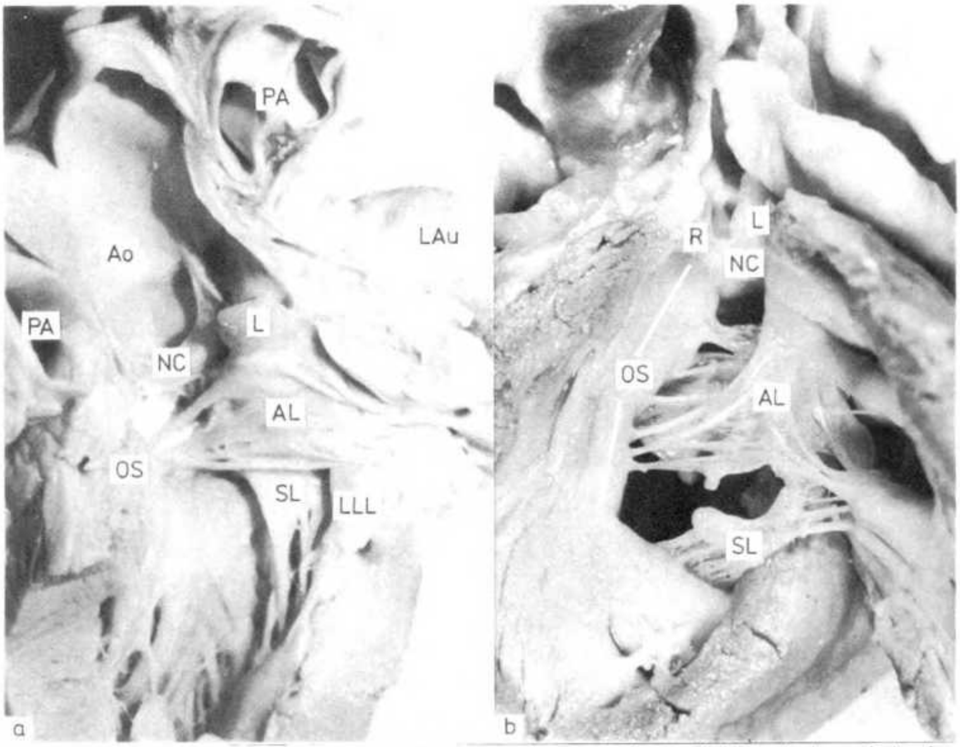

Fig. 4 *(a) Left ventricular view of a small AVSD (the same heart as in Fig. 1). The left valve is attached to the rim of the outlet septum. The defect of the inlet septum (transilluminated), although quite small, is large enough to cause the abnormal orientation and attachment of the valve leaflets. PA, pulmonary artery. (b) Left ventricular view of large AVSD. There is no inlet portion and the outlet septum is very attenuated. The inlet deficit extends above, below, and behind the left valve. The anterior leaflet of the valve is attached by secondary chordae tendineae to the rim of the outlet septum, while those of the septal leaflet insert into the summit of the remaining septum. Other abbreviations as in Fig. 1.*

malities. These are the abnormal plane of the atrioventricular valve(s), which are attached at the same point to the septum (Fig. 1a, b), the loss of anteroposterior dimension to the left ventricular outflow tract (Fig. 2a, b), and the abnormal position of the aortic valve. This structure is no longer wedged between the ventricular inlets, but lies anterior and superior to the atrioventricular valve leaflets (Fig. 2b, 4b). All these features indicate defective development of the inlet septum and absence of its atrioventricular component. Specimens without an interatrial communication ("canal-type" ventricular septal defects) have in the past been excluded from the compass of the malformation under review[32] but, if there is a disproportion between the inlet and the outlet lengths of the left ventricle, they can be classified as examples of atrioventricular septal defect.[7]

(2) ATRIOVENTRICULAR VALVES

Because the valves develop from the posterior wall of the embryonic heart and some elements of the inlet/outlet cushions they are obligatorily malformed when the embryonic structures develop abnormally. Their myocardial origin is often suggested by the muscular anomalies of both chordae tendineae and papillary muscles in atrioventricular septal defect (Fig. 5). Valve morphology accords with the degree of posterior septum deficit—two orifices usually occur with a fairly small defect and the severest form of the malformation has the free floating leaflets of the common valve sometimes predominantly opening into one or other ventricle and the huge defect both behind, below, and in front of the common valve (Fig. 4b). The plane of the valves or valve, always abnormal in atrioventricular septal defect, is governed in part by the size of the remnant of the inlet septum. Usually the valves are attached to this structure so that they "descend" to an undue extent into the ventricles. Thus there is a gap where the septum should be, and interatrial or ventriculoatrial shunting occurs through this gap.

Ventriculoatrial shunting may also occur through

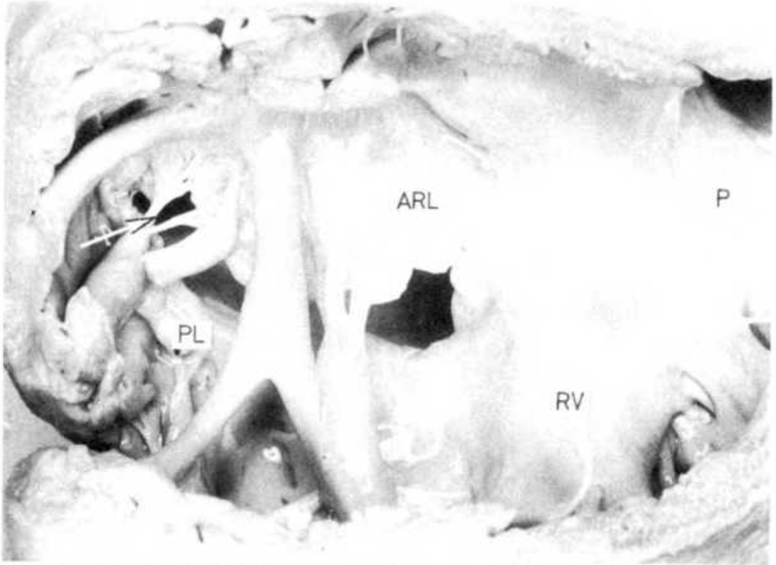

Fig. 5 *The right valve in AVSD, right ventricular view. The valve leaflets are supported mainly by muscle. There are truly tendinous cords only at the right lateral-posterior commissure (arrowed). Most of the remaining tensor apparatus is muscular. P, pulmonary valve; RV, right ventricle; PL, posterior leaflet; ARL, anterior right leaflet.*

the "cleft" in the left valve. The disposition of leaflet tissue is abnormal in atrioventricular septal defect so that the left valve leaflets are abnormally orientated. The anterior leaflet itself is not cloven but is always intact—the cleft is the tissue deficit between the anterior and posterior (septal) leaflets of the valve (Fig. 6a, b). The degree of deficit, however, does not necessarily influence the function of the valve.[35]

Double orifice left atrioventricular valve results from an extra deep scallop (cleft) between either the anterior and lateral or the lateral and posterior leaflets, respectively, and a bridge of tissue between the two leaflets. Deep scallops (clefts) are sometimes found in normal hearts, especially in the tricuspid valve,[36] and reflect the undermining process which modelled them.

Parachute mitral valve, present in about 7% of cases,[37] results from inadequate liberation of the future papillary muscles from the posteromedial embryonic wall.

(3) AORTIC OUTFLOW TRACT

The pathognomonic appearance of the left ventricular outflow tract results from posterior septal deficiency (the "scooped-out" appearance)[5 6] and the abnormal attachment, often with short, thick chordae,[38] of the anterior left leaflet to the remaining outlet septum. Because this septum does not have its normal smooth continuity with the infundibular septum, the myocardium in the outflow tract attenuates, giving the characteristic tunnel-like outflow tract (Fig. 4b).

The displacement of the aortic valve is probably real; if the atrioventricular septum is absent, then the aortic valve is further superior and to the right than in normal hearts, as it is no longer wedged between the two atrioventricular valves.

(4) PULMONARY OUTFLOW TRACT

Fallot's tetralogy and atrioventricular septal defect are an uncommon combination; the hypothesis offered concerning the inlet septal maldevelopment does not contradict the generally accepted views about the ontogeny of the infundibular malformation.[33 34]

(5) ATRIAL SEPTUM

The atrial septum is often normally developed in atrioventricular septal defect, and this also lends support to the view that the malformation concerns the ventricular septum. None of the widely accepted views about atrial septation is challenged—rather, these views are supported. Defective atrial septation has never satisfactorily explained atrioventricular septal defect. Despite the usual cognomen "atrioventricular canal" the malformation does not remotely resemble the arrangement in the newly-looped embryonic heart. Arrested or abnormal development of this region cannot explain the malformation of the outflow tract of the left ventricle, which may be mild or severe, but is always present.

Common atrium does, of course, represent rudimentary atrial septation, and is usually associated

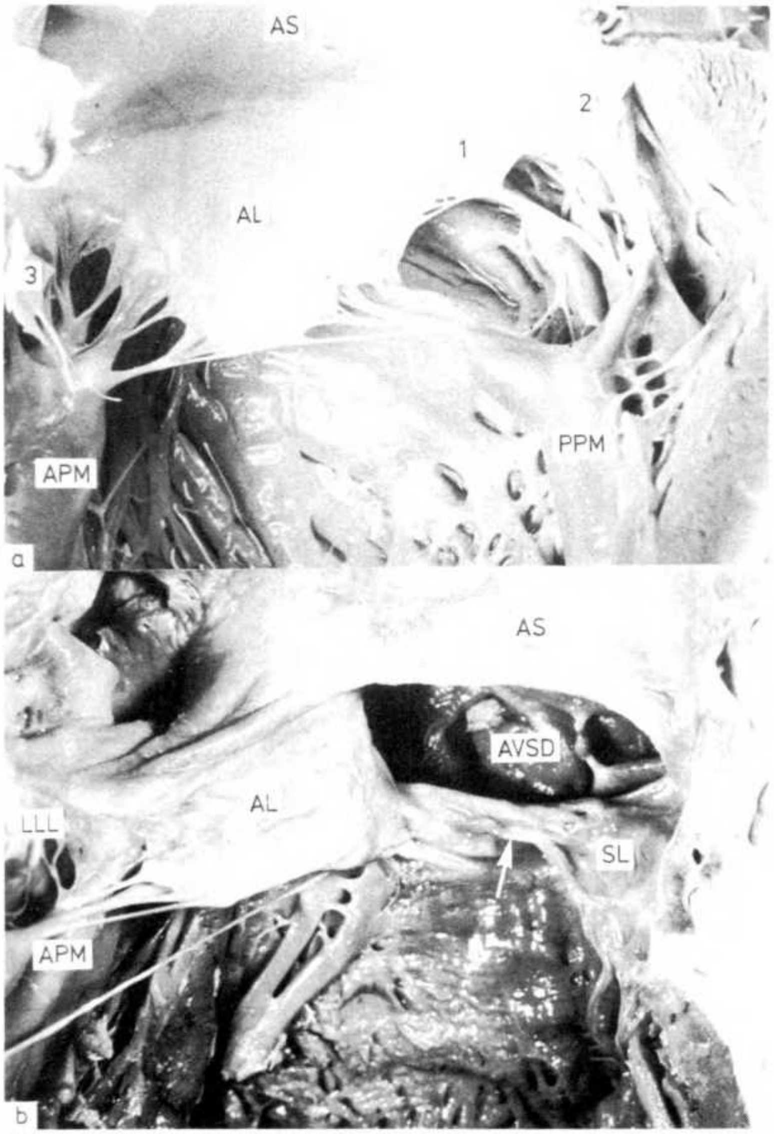

Fig. 6 *(a) The left ventricular inflow in the normal heart. The anterior mitral leaflet is supported by both papillary muscles; the posterior leaflet is characteristically scalloped (1, 2, 3). The anterior leaflet completely covers the upper third of the ventricular septum and leaflet tissue is continuous around the annulus. (b) Left ventricular inflow in AVSD. The anterior leaflet of the left valve is almost at right angles to the normal structure in (a) so that the upper third of the ventricular septum is visible. The leaflet is supported only by the anterior papillary muscle group—the remainder of the leaflet inserts into the posterior wall of the outlet septum. Distinct septal and lateral leaflets are recognised. Although there is valve tissue on the summit of the ventricular septum there is a gap (the cleft, arrowed) between the anterior and septal leaflets. The anterior leaflet is never split—clefts are the spaces between the leaflets. PPM, posterior papillary muscle group; APM, anterior papillary muscle group. Other abbreviations as in Fig. 1.*

with the more severe forms of atrioventricular septal defect (Fig. 6). There seems no reason to suppose any more elaborate mechanism than defective atrial septation to explain this coexistence.

Conclusion

The embryological studies reviewed here shed light on the developmental background of the ventricular septum and the atrioventricular valves. The embryology of the anatomical touchstones of atrioventricular septal defect has been hypothesised, and this hypothesis challenges neither the accepted views about atrial septation nor about outflow tract maldevelopment which may coexist.

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Extra echo spaces: ultrasonography and computerised tomography correlations

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SUMMARY Among the echocardiograms of 844 patients of the International Goodwill Hospital from January 1980 to April 1981, 700 showed clinically inexplicable extra echo spaces. Fifty of the 700 had computerised tomography of their hearts which showed the extra echo spaces to be caused either by anterior or posterior subepicardial fat. Six of the 50 cases had both fat and pericardial effusions, which are difficult to differentiate echocardiographically unless follow-up clinical observations are performed. Subepicardial fat deposits are reasonable explanations for the extra echo spaces frequently observed by echocardiography: they correlate well with clinical findings. Subepicardial fat should be recognised as the cause of such extra echo spaces.

Echocardiography has contributed to the clinical diagnosis of pericardial effusions ever since the latter were quantitatively evaluated according to the sizes and characteristics of their "echo-free spaces".[1] It was also postulated that, in some cases, small amounts of pericardial fluid could be detected by echocardiography, even fluid in physiological quantities in normal subjects. Is echocardiography sufficiently sensitive to detect such small amounts of pericardial fluid? Can such small quantities of fluid actually produce images showing several millimetres separation of the epicardium from the pericardium posteriorly, permitting echocardiographic assessments?

The hypothesis that "echo-free spaces" represent pericardial effusions is based on the assumption that a dense, broad, band-like echo behind the posterior wall of the left ventricle is the pericardial echo, and that the curvilinear echo above the "echo-free spaces" is that of the epicardium. The epicardium consists of a single layer of mesothelial cells[2]; the pericardium is about 1 mm thick.[3] Therefore, it is reasonable to assume that the epicardium alone cannot produce a curvilinear echo and that the pericardium alone is not likely to produce a dense, broad, band-like echo on echocardiography. Furthermore, "echo-free spaces" have not been clearly defined. In asymptomatic persons, inexplicable extra echo spaces are often identified behind the posterior wall of the left ventricle, which may be relatively echo free or even echo dense on comparison with the density of the myocardium. Using an automatic gain control or proper gain damping, however, these spaces usually become echo free. Were we to assume that all such extra echo spaces behind the posterior wall of the left ventricle are the result of pericardial effusions, the frequency of pericardial effusions would appear to be much greater than we know it to be. Furthermore, our experience indicates that in many cases, these extra echo spaces do not correlate with the clinical findings of pericardial effusions, and they fail to respond to treatment during lengthy follow-up studies (Fig. 1).

The question arises as to what these extra echo spaces represent and why they are so frequently observed echocardiographically. In some instances preoperatively encountered posterior extra echo spaces cannot be confirmed at operation as being caused by pericardial effusions. Identical extra echo spaces continue to present themselves in uncomplicated postoperative patients. Extra echo spaces may in such cases be the result of normal structures with characteristics similar to pericardial fluid, such as fat surrounding the heart. This hypothesis was proposed for this investigation.

Computerised tomography is a reliable noninvasive means of distinguishing pericardial fluid from fat since the fluid produces positive computerised tomography values and the fat produces negative computerised tomography values.[4 5] Therefore, computerised tomography was used in the present study to assist in determining the cause of the extra echo spaces detected echocardiographically.

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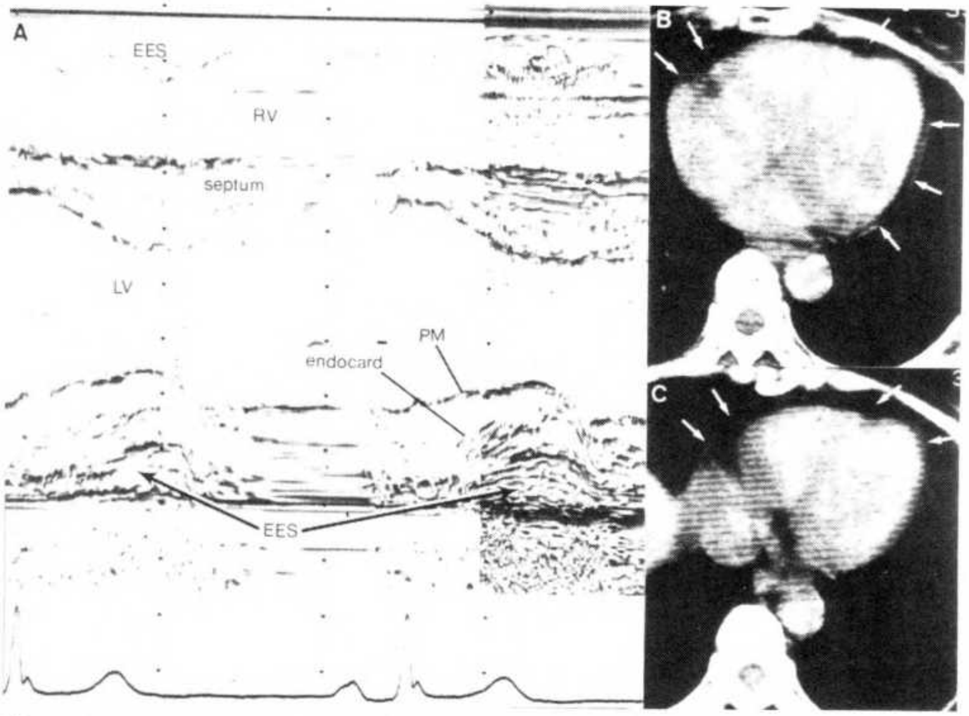

Fig. 1 *A 70-year-old Japanese woman with ischaemic heart disease and hypertension.* (A) *Her echocardiograms consistently showed dense extra echo spaces both anteriorly and posteriorly which became relatively echo free using automatic gain control.* (B) *and* (C) *Computerised tomography scans show a linear band encircling the heart, representing the thin pericardium-epicardium (white arrows). There is no evidence of pericardial effusion. Between the thin pericardium-epicardium and the heart, a broad lucent-appearing zone indicates subepicardial fat anteriorly and posteriorly. The extra echo spaces on the echocardiogram are attributed to fat, not to an effusion (courtesy of Dr Satoshi Ohta). EES, extra echo spaces; RV, right ventricular cavity; septum, interventricular septum; LV, left ventricular cavity; PM, papillary muscle; endocard, endocardium.*

Method

From January 1980 to April 1981, 844 in- and outpatients of the International Goodwill Hospital received 1497 echocardiographic examinations. The echocardiography was performed by one of the authors (MH) using an Aloka model SSD-110 unit, and included strip chart tracings. In each case, a 2·25 MHz transducer was placed at the fourth intercostal space at the left parasternal region for M-mode scanning from the aorta to the cardiac apex. Technical errors which can produce "false echo-free spaces" were thus avoided.[6 7] Automatic gain control was used in all tracings to delineate clearly the border zone echoes. The posteriorly located extra echo spaces imaged here were those behind the posterior wall of the left ventricle, and were identified in the vicinity of scarcely visible mitral echoes.

After omitting 144 cases with poorly identified posterior left ventricle walls, the remaining 700 cases were analysed. Variations in sizes and locations of the extra echo spaces were assessed during interpretation of the echocardiograms. When repeated recordings were made of the same patients, extra echo spaces were consistently observed. The posteriorly located extra echo spaces were categorised as systolic, and systolic and diastolic combined.

Among the 700 cases, the 50 most recently examined were studied using a Varian model V-360-3 computerised tomography scanner, with 3·6 second scan. Without contrast media, computerised tomography scans were made of the heart at 12 different levels, from aorta to the cardiac apex. The computerised tomography values were recorded in the region of the heart below the level of the mitral valve. The 50 patients ranged in age from 37 to 84 years, with a mean of 64 years. There were 29 women and 21 men. Among the 50 patients, 21 had ischaemic heart disease with or without hypertension: 10 with cardiomyopathy, four with atrial septal defects, three with valvular heart disease, two with collagen disease, and one each, pulmonary hypertension, aortitis, pericarditis, renal hypertension, and arrhythmia. The remaining five cases did not have cardiac disease.

Height weight ratios were calculated for each patient according to Broca's index.

Results

Anteriorly located extra echo spaces were observed in 607 cases (86·7%). In 229 (32·7%), posteriorly located extra echo spaces occurred only during systole. In 200 cases (28·5%), extra echo spaces occurred in both systole and diastole (Table). The 429 cases with posterior extra echo spaces all had anterior extra echo spaces.

Table *Extra echo spaces by age*

Decade	*No. of patients*	*Extra echo spaces*		
		Anterior	*Posterior*	
			Systolic	*Systolic/ diastolic*
0–9	9	0	0	0
10–19	32	15 (46·8%)	0	0
20–29	57	33 (57·8%)	7 (12·2%)	0
30–39	98	79 (80·6%)	25 (25·5%)	13 (13·2%)
40–49	158	146 (92·4%)	69 (43·6%)	40 (25·3%)
50–59	139	135 (97·1%)	60 (43·1%)	49 (35·2%)
60–69	101	97 (96·0%)	42 (41·5%)	37 (36·6%)
70–79	82	78 (95·1%)	23 (28·0%)	42 (51·2%)
80–89	24	24 (100%)	3 (12·5%)	19 (79·1%)
Total	700	607 (86·7%)	229 (32·7%)	200 (28·5%)

All 50 patients who had computerised tomography scans had both anterior and posterior extra echo spaces echocardiographically. In 21 cases, posteriorly located extra echo spaces occurred only during systole. In the remaining 29 cases, extra echo spaces occurred in both systole and diastole. The dense, broad, band-like echo occurring behind the posterior wall of the left ventricle is that of "pericardium"; its systolic movements were nearly imperceptible in 11 cases, suggesting the presence of pericardial effusions.[1] In the remaining 38 cases, minimal "pericardial" motion occurred parallel to the systolic movements of the posterior wall of the left ventricle.

Computerised tomography disclosed fat around the hearts of the 50 patients scanned, accounting for the extra echo spaces on their echocardiograms. The computerised tomography values of these fat deposits varied from −36 to −115, with a mean of −87, clearly distinct from those of pericardial effusions which had positive computerised tomography values from 0 to +40, depending upon the components of the effusions.[5] The fat deposits were subepicardial anteriorly in all 50 cases. They were also posteriorly subepicardial in 18 cases. The relatively few cases with posterior rather than anterior subepicardial fat were the result either of a masking effect by the overlying lung or of vigorous movements of the posterior wall of the left ventricle. It did not necessarily indicate that less fat was present posteriorly. The computerised tomography of the 50 patients indicated that six had both pericardial effusions and fat. Imperceptible "pericardial" movement was encountered on the echocardiograms of five of the six, and in six other cases with only fat surrounding their hearts. This suggests that imperceptible "pericardial" movement is not a reliable criterion for diagnosing pericardial effusions.

Posterior subepicardial fat was clearly visible when pericardial effusions were present, but as the effusions resolved, the posteriorly located fat was rendered indistinct for the reasons previously mentioned. Computerised tomography could clearly distinguish fat from effusions, but echocardiography could not clearly differentiate the extra echo spaces caused by the two conditions.

According to Broca's index, seven patients were overweight and two were underweight, but there were no significant correlations between the extra echo spaces and the patients' obesity.

Discussion

Echocardiography has facilitated the diagnosis of pericardial effusions. In 1972, an attractive hypothesis was advanced that the extent of pericardial effusions could be estimated according to the sizes and shapes of their "echo-free spaces".[1] Though many investigators have tested this hypothesis, reports of follow-up studies of pericardial effusions are unavailable, particularly any with evidence of complete resolution of "echo-free spaces" after treatment. An illustrative case of acute myocarditis with pericardial effusion was reported in the first[1] but not the subsequent editions of one text.[8, 9] Others have reported cases before and after dialysis[10, 11] and one of tuberculous pericarditis with effusion.[12] Though "echo-free spaces" of these cases decreased in extent, they did not resolve completely. Constrictive pericarditis was the only explanation offered for residual "echo-free spaces".[12]

Horowitz *et al.*[13] reported anterior "echo-free spaces" despite pericardial fluid in volume of 16 ml or less, confirmed at surgery. They pointed out that anterior "echo-free spaces" caused by pericardial effusions are most unusual. The nature and cause of such "echo-free spaces" have not been explained. One investigator was reluctant to diagnose pericardial effusions in patients with only anterior "echo-free spaces".[1, 8, 9] A small pericardial effusion, however, often forms anterior to the heart rather than posteriorly because of the effect of gravity on the heart

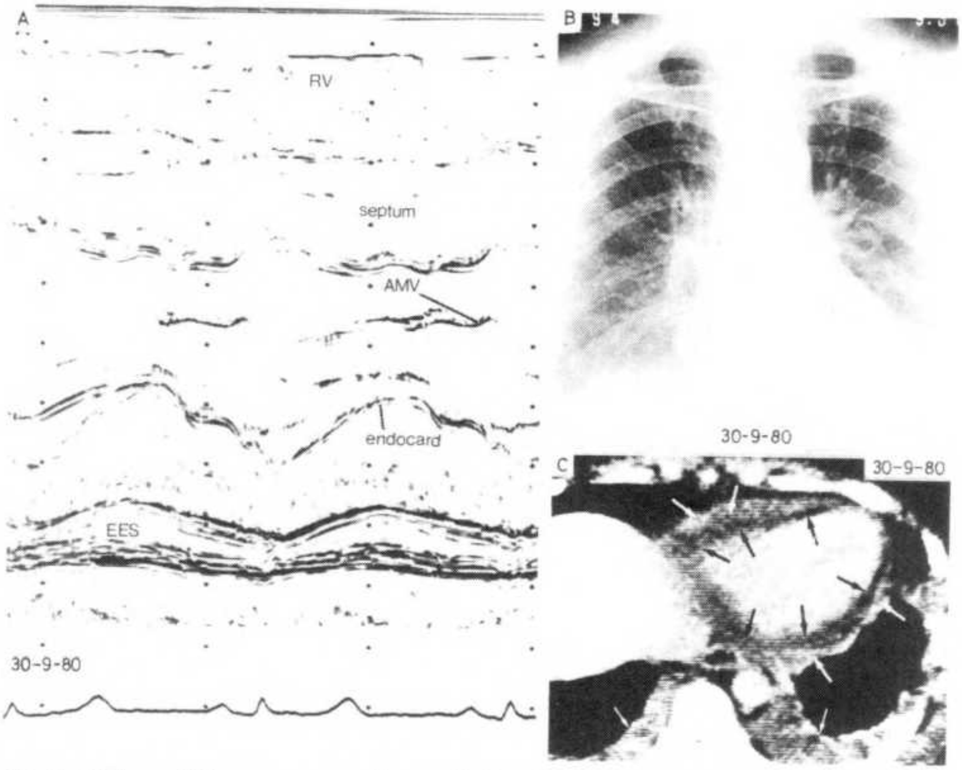

Fig. 2 *A 53-year-old Japanese woman with congestive heart failure caused by renal hypertension.* (A) *Her echocardiogram (speed: 100 mm/s with automatic gain control) shows that the anterior mitral valve echoes are scarcely visible. The image in the posterior portion of this echocardiogram represents the posterior wall of the left ventricle. There are distinct extra echo spaces posteriorly, and behind the posterior one is a dense, broad, band-like echo whose minimal movement is parallel to the systolic movements of the left ventricle, suggesting a moderate pericardial effusion.* (B) *A posteroanterior* (PA) *chest radiograph the same day as echocardiography shows an increased cardiothoracic ratio and bilateral pleural effusions.* (C) *A computerised tomography scan the same day as echocardiography and chest radiography shows a shadow surrounding the heart, indicative of moderate pericardial effusion (white arrows), much greater in extent anteriorly than posteriorly because of posterior shift of the heart caused by gravity. The radiolucent zone surrounding the heart is caused by subepicardial fat (black arrows). Since the posteriorly located fat is much greater in extent than the effusion, a greater portion of the posterior extra echo spaces on echocardiography is caused by fat than by effusion. The bilateral pleural effusions detected radiographically were confirmed by computerised tomography (small white arrows). RV, right ventricular cavity; septum, interventricular septum; AMV, anterior mitral valve; endocard, endocardium; EES, extra echo spaces.*

(Fig. 2, 3, and 4). Ideally, echocardiography should detect such a small pericardial effusion.

Posterior "echo-free spaces" are attributed to pericardial effusions based on assumptions that a dense, broad, band-like echo behind the posterior wall of the left ventricle is of pericardial origin, and the curvilinear echo above the "echo-free spaces" is caused by the epicardium. If the former assumption were true, such an echo would not occur with complete absence of the left pericardium. In each of four cases of complete absence of the left pericardium, we observed identical dense broad band-like echoes behind posterior wall of the left ventricle[14] (Fig. 5). These echoes could not have represented the pericardium. Other investigators have reported similarly.[15-17] The epicardium consists of a single layer of mesothelial cells only 5 to 6 μ thick, and it would be unusual for such a thin layer to produce a recognisable echo on echocardiography. There is some connective and areolar tissue beneath the epicardium,[2] and the epicardium and this connective tissue apparently play a role in producing the so-called "epicardial echo". The areolar tissue contains varying amounts of fat, blood vessels, and nerves. Anatomically, the thickness of this tissue has not been measured, but radiographically, it is 2 mm thick in 75% of adults.[18] The

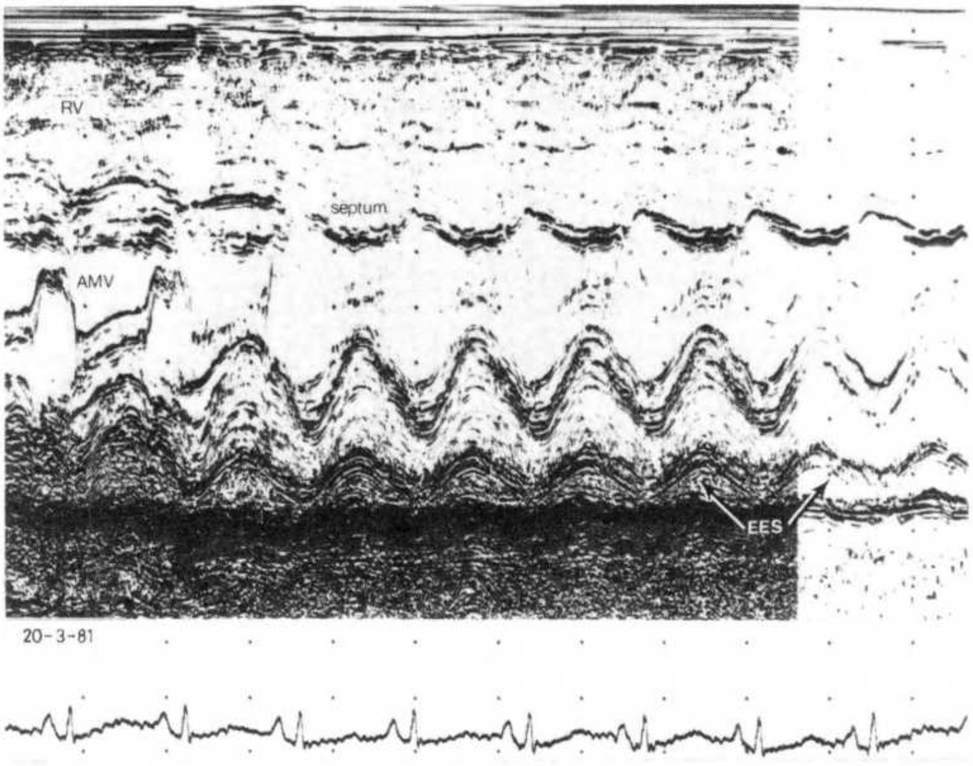

Fig. 3 *M-mode scan of the same patient six months later. Continuity of the ventricular septum and the anterior mitral valve echoes is normal. Posteriorly located extra echo spaces are echo dense and become echo free with automatic gain control. The dense broad band-like echo behind the posterior wall of the left ventricle moves minimally, parallel with systolic motion of the left ventricle. The anterior and posterior extra echo spaces are indistinguishable from those seen six months earlier. RV, right ventricular cavity; septum, interventricular septum; AMV, anterior mitral valve; EES, extra echo spaces.*

subepicardial fat can be appreciable in quantity and can mimic cardiomegaly on chest radiography. Chest surgery, however, is necessary to prove the nature of such apparent cardiomegaly.[19 20] Accordingly, it may be assumed that a thick layer of subepicardial fat can produce extra echo spaces on echocardiography. This is supported by results of experimental echocardiography in which two or more linear echoes issued from a strip of myocardium containing subepicardial fat.[21] The first linear echo was said to be of epicardial origin, but the investigators did not speculate about the origin of the later echoes. We believe that the first linear echo originated from the border between the epicardium and areolar tissue. It is followed by an "echo-free space" caused by fat. The second linear echo in the "echo-free space" is attributed to the coronary vessels. The last linear echo is probably the result of the border between areolar tissue and myocardium.

In the present study, differences in computerised tomography values clearly showed that the extra echo spaces were the result of pericardial and/or subepicardial fat, rather than of effusions. Accordingly, the dense broad band-like echo behind the posterior wall of the left ventricle is a fusion echo of the epicardium and subepicardial tissue, the pericardium, and the pleura. The former two tissues comprise the potential pericardial cavity which is not visualised except in cases of effusions. Anterior to the dense broad band-like echo is another extra echo space caused by subepicardial fat, and there may be scattered miliary echoes resulting from coronary vessels and nerves. The superior portion of the extra echo spaces is demarcated by a curvilinear echo produced at the junction between subepicardial fat and myocardium. This curvilinear echo has been misinterpreted as an epicardial echo. The fat-producing extra echo spaces were thought to represent the pericardial cavity rendered visible by effusions. The concept that fat produces extra echo spaces had not been reported

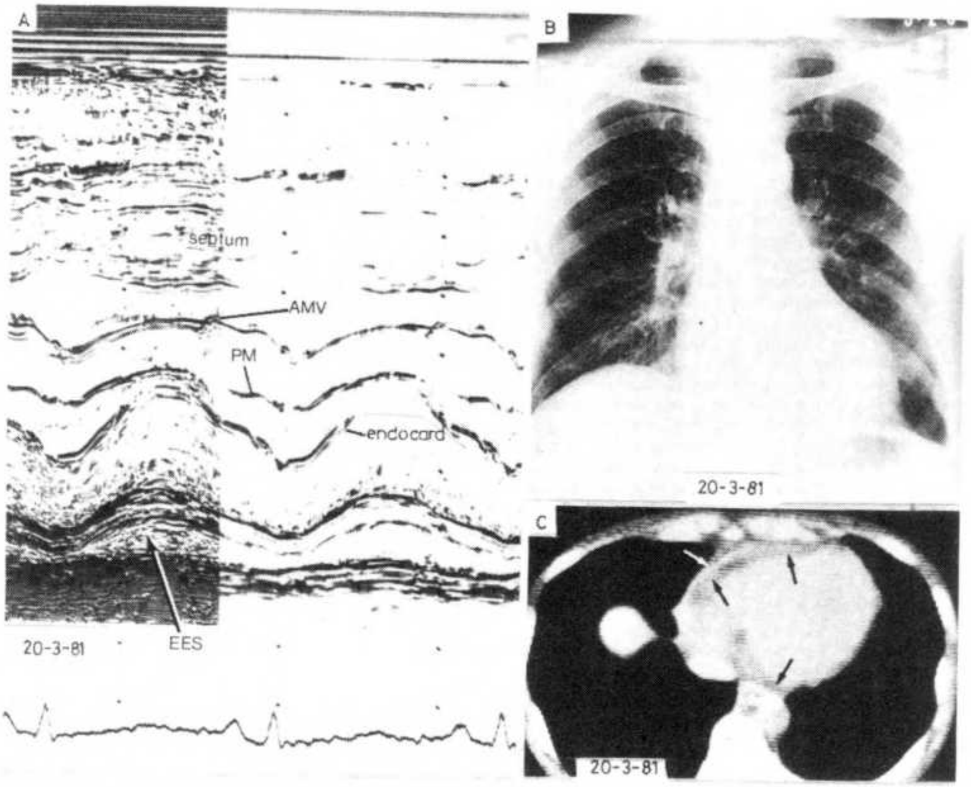

Fig. 4 (A) *High speed echocardiogram the same day as Fig. 3 shows an extra echo space behind the posterior wall of the left ventricle which became "echo-free" with the aid of automatic gain control. Size and contour were unchanged since the initial examination of 30-9-80. The extra curvilinear echo in the "echo-free spaces" is probably the result of coronary vessels.* (B) *PA chest radiograph of 20-3-81 shows a decrease in cardiac size and no pleural effusion.* (C) *A computerised tomography scan on 20-3-81 shows that the previously observed pericardial effusion resolved except for a minimal effusion near the anterior portion of the heart (white arrow), causing an increased width of pericardium-epicardium silhouette. The posteriorly located subepicardial fat is no longer visible, because of resolution of the pericardial effusion. Anterior subepicardial fat (black arrows) remains visible and is greater in extent than the pericardial effusion. Though the posterior subepicardial fat is not visible on the computerised tomography scan, there is no evidence of pericardial effusion posteriorly. Thus, the posterior extra echo space visualised echocardiographically is not the result of a pericardial effusion. This is a good example of residual extra echo spaces after the treatment and resolution of a pericardial effusion. Septum, interventricular septum; AMV, anterior mitral valve; PM, papillary muscle; endocard, endocardium; EES, extra echo spaces.*

except for brief suggestions in texts,[1 8 9 22] relating to anterior extra echo spaces. Assuming that fat surrounding the heart can cause extra echo spaces, the residual "echo-free spaces" still visible after successful treatment of pericardial effusions are easily explained.

Increased accumulation of subepicardial fat occurs during the aging process,[3] as was observed in the present study. Patients under 9 years of age had neither anterior nor posterior extra echo spaces. Adolescents had only anterior extra echo spaces. Posterior extra echo spaces were observed in only 12·2% of patients between the ages of 20 and 29 years. Both anterior and posterior extra echo spaces increased in frequency after the age of 29 years. Complete resolution of the extra echo spaces of a patient with acute myocarditis has been reported[1] and was probably a young individual, without residual extra echo spaces caused by excessive fat around the heart. In our series of pericardial effusions, only one patient, a 43-year-old emaciated Japanese man with tuberculous pericardial effusion, displayed complete resolution of his extra echo spaces. Corticosteroids can enhance the accumulation of subepicardial fat,[3] but none of the patients in the present study received such treatment.

In a variety of heart diseases, posteriorly located

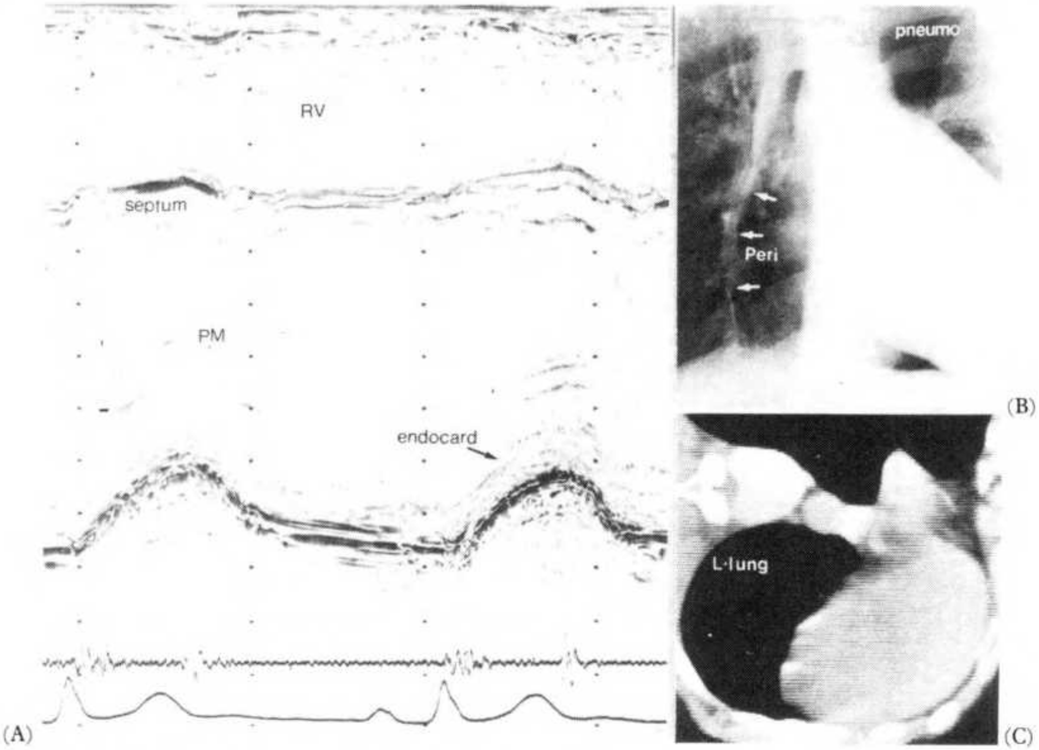

Fig. 5 *A 33-year-old Japanese man with congenital complete absence of the left pericardium.* (A) *Echocardiogram showing hyperkinetic movements of posterior wall of the left ventricle and paradoxical movement of the ventricular septum – the usual manifestations of this abnormality. The dense broad band-like echo behind the posterior wall of the left ventricle is indistinguishable from that normally seen. Since the left pericardium is absent, the dense broad band-like echo cannot be a pericardial echo. It is attributed to thickening of the epicardium and the connective tissue beneath it.* (B) *PA chest radiograph after a left pneumothorax resulting in a pneumopericardium on the right (white arrows) caused by absence of the left pericardium-parietal pleura.* (C) *A computerised tomography scan in the left lateral decubitus position shows that the heart descends to the left thoracic wall, indicating complete absence of the left pericardium. There were no densities indicative of pericardium-epicardium on the left side at any level of the computerised tomography scans. RV, right ventricular cavity; septum, interventricular septum; PM, papillary muscle; endocard, endocardium; Peri, pericardium; pneumo, pneumothorax; L lung, left lung.*

extra echo spaces are reflected by echo-dense or echo-free patterns. No explanations have been offered for the cause of such spaces,[23] though in echocardiographic texts, similar findings have been reported to be the result of factors other than pericardial effusions. In the majority of such cases, improper gain damping was used, resulting in a poorly demarcated border zone, and the extra echo spaces were overlooked. To image the posterior "echo-free spaces" clearly, the examiner must always anticipate such lesions, using proper gain damping in each case. Automatic gain control enables the "echo-free spaces" to be imaged without much effort. In fact, since our preliminary reports,[24 25] the rate at which we have detected extra echo spaces has increased nearly tenfold with the routine use of automatic gain control. The frequencies of posterior extra echo spaces reported in Japanese texts varied from 8·7% to 49%, with a mean of 24·2%[12 16 17 26–28]; whereas, in English texts, their frequencies varied from 5% to 17·2%, with a mean of 9%.[9–11 29–33] The reason for these differences is not clear, but they probably arise from the use of a variety of echocardiographic units of different manufacture, and the various interests of the investigators involved. A very improbable explanation is that Japanese have more fat around their hearts than Americans. Least likely is the possibility that some of our tracings were made too medially to image the posterior wall of the left ventricle, and that the extra echo spaces in the present study were artefacts. When tracings are made too medially, however, the continuity of the mitral valve echoes is lost, and multiple-layer echoes result.

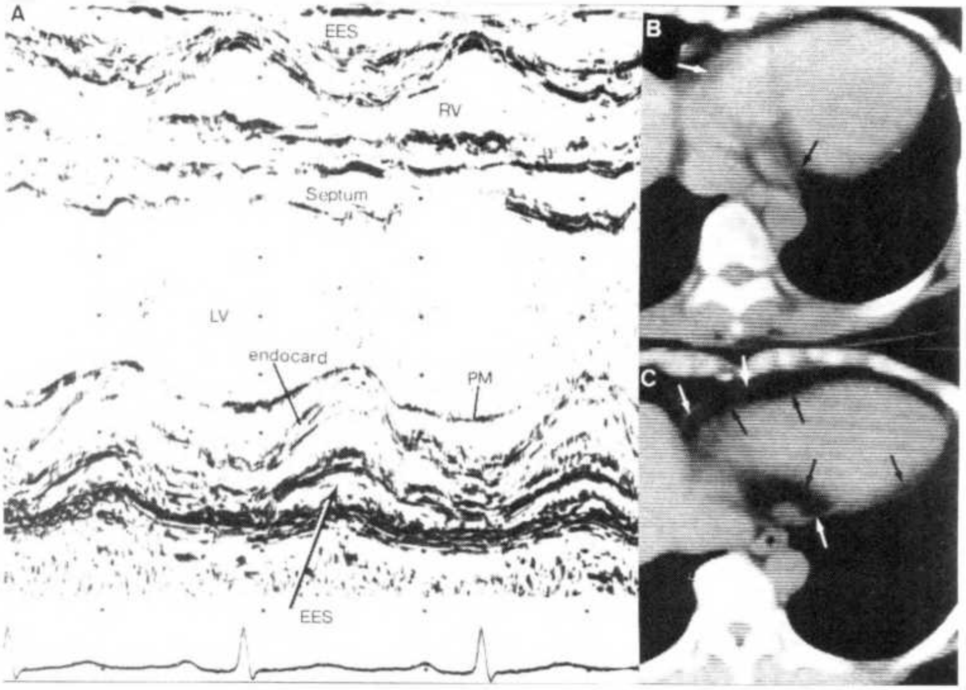

Fig. 6 *A 58-year-old Japanese woman with ischaemic heart disease with hypertension.* (A) *Her echocardiograms consistently showed both anterior and posterior extra echo spaces. Though she was asymptomatic, her chest radiographs indicated that her heart was enlarged.* (B) *and* (C) *computerised tomography showed considerable pericardial fat anteriorly, and subepicardial fat both anteriorly and posteriorly (black arrows). The pericardium-epicardium image is thin* (*white arrows*), *indicating that there was no pericardial effusion. EES, extra echo spaces; RV, right ventricular cavity; septum, interventricular septum; LV, left ventricular cavity; PM, papillary muscle; endocard, endocardium.*

In the present study, we took great care in using M-mode scanning from the aorta to the cardiac apex in each case. Therefore, the extra echo spaces observed could not have been caused by artefacts; they are attributed to fat around the heart.

The present study correlated the computerised tomography images of pericardial and/or subepicardial fat with the extra echo spaces imaged by echocardiography. There is adequate explanation for the extra echo spaces frequently observed in the asymptomatic patient (Fig. 6), and the persistent extra echo spaces observed during follow-up studies of successfully treated pericardial effusions. Thus, fat around the heart can produce extra echo spaces indistinguishable from those of pericardial effusions. The echocardiographic diagnosis of pericardial effusions is therefore difficult, unless they occur in relatively young patients without appreciable fat posteriorly, or in massive effusions which cause pendulum-like cardiac motion.

Finally, the extra echo spaces caused by fat can outline the space between the epicardium and myocardium, but not the pericardial space which is outlined by pericardial effusions. The extra echo spaces can be either echo dense or echo free; thus the term "echo-free spaces" is confusing. For the benefit of students and those beginning as echocardiographers this term should not be used.

The authors thank Dr Walter J Russell for reviewing the manuscript and for his editorial suggestions.

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Echocardiographic features of impaired ventricular function in diabetes mellitus

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SUMMARY In order to study left ventricular diastolic function in diabetes mellitus, simultaneous echo- and phonocardiograms were recorded in 142 diabetics (free from heart disease), 20 normal subjects, and 16 patients with coronary artery disease. The resultant traces were digitised, and left ventricular relaxation and the rate and duration of cavity dimension increase and wall thinning were determined. Diastolic variables of left ventricular function were normal in 12 young diabetics with no complications. Significantly delayed mitral valve opening relative to minimum dimension and aortic valve closure was found in all other groups of diabetics. Forty-four diabetics with severe microvascular complications had significantly reduced peak rate and prolonged duration of wall thinning and dimension increase. The abnormalities were unlike those found in subjects with coronary artery disease.

The extent of microvascular complications was significantly correlated to most variables of diastolic function. This relation was maintained in 31 diabetics with significant cavity dimension increase during isovolumic relaxation (incoordinate relaxation). In 42 juvenile onset patients there was good correlation between the duration of diabetes and most variables of diastolic function.

These studies show that the primary cardiac abnormality in diabetic micro-angiography is a prolonged duration and reduced rate of posterior wall thinning with impaired left ventricular dimension increase, reflecting abnormal myocardial properties.

Impaired left ventricular function may frequently be detected in asymptomatic diabetics.[1] It is related to the presence and extent of diabetic microvascular complications and the duration of diabetes, and is presumably the result of specific diabetic myocardial involvement.[2] Although systolic time intervals are abnormal in some diabetics,[1–5] they have a complex underlying mechanism and are more frequently abnormal in diabetics with associated disorders such as hypertension, coronary artery disease, and heart failure.[1] The studies of Sanderson *et al.*[6] and Shapiro *et al.*[1 2 5] suggest that impairment of some aspects of diastolic function is common and may be the primary abnormality in diabetes; the purpose of the present paper is to extend previous studies of diastolic left ventricular function by detailed examination of relaxation, cavity filling, and wall thinning using computerised interpretation of manually digitised echocardiograms.

Patients and methods

Patients and control subjects have previously been described in detail.[1 2] From 473 diabetics, aged 16 to 60 years, 185 were selected as free from clinical heart disease, hypertension (diastolic blood pressure above 100 mmHg), and conditions known to influence left ventricular function. Of these, 142 had echocardiograms which were suitable for the computerised analysis (79 men and 63 women, mean age 41±9 years); 42 of these were insulin-dependent diabetics who developed the disease before the age of 20 in whom the clinical presentation of diabetes was assumed to represent its onset. These 42 patients were used to determine relations to the duration of diabetes (mean duration of diabetes 9±8 years, range 0 to 25 years).

The 142 diabetics were subdivided into the following groups:

(i) Diabetics with no complications (n=39).

(ii) Diabetics with mild microvascular complications, mild background retinopathy, and/or mild proteinuria (n=47).

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(iii) Diabetics with severe microvascular complications, heavy proteinuria, and/or proliferative retinopathy (n=44).

(iv) Recently diagnosed (within three years) young insulin-dependent diabetics (n=12).

The 142 diabetics were graded according to the presence and extent of complications and an index of microvascular complications was constructed by summation of the individual scores for each complication subgroup (Table 1) which allowed for a scale from zero (with no complications, as in groups (i) and (iv)) to seven (when all were present and severe as in some patients in group (iii)).

Table 1 *Scheme for grading microvascular complications*

Code	
	Retinopathy
0	None
1	Mild background: less than 10 red dots per eye
2	Severe background: greater than 10 red dots per eye
3	Proliferative
	Proteinuria
0	None
1	Mild: one or two plus proteinuria
2	Severe: heavy proteinuria
	Neuropathy
0	None
1	Mild: absent ankle jerks and vibration sense in feet
2	Severe: further evidence of neuropathy including autonomic neuropathy

Two groups were selected as controls:

(i) Twenty normal subjects, 10 men and 10 women (mean age 39±11 years) from members of hospital staff, and patients undergoing investigation of atypical chest pain who had normal coronary and left ventricular angiograms.

(ii) Sixteen patients with typical angina of exertion (nine men and seven women, mean age 40±8 years), from those undergoing investigation of chest pain. All had significant coronary atheroma on angiography and none was taking beta-adrenergic blocking agents.

Echocardiography with simultaneous electrocardiogram (standard lead II) and phonocardiogram to determine onset of high frequency component of the aortic heart sound (A_2) was performed in the partial left lateral position with an SK20 ultrasonoscope and a Cambridge multichannel photographic recorder, paper speed 100 mm/s. A left ventricular echocardiogram at the level of the tips of the mitral valve showing clear continuous echoes from both the septum and posterior wall endo- and epicardium was used for further analysis (Fig. 1).

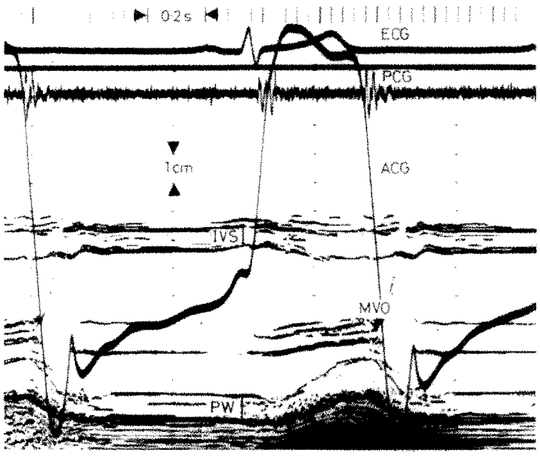

Fig. 1 *Normal left ventricular echocardiogram with simultaneous phonocardiogram (PCG), electrocardiogram (ECG), and apexcardiogram (ACG). MVO, mitral valve opening; IVS, interventricular septum; PW, posterior wall.*

Echocardiographs were digitised as previously described by Gibson and Brown,[7] using a Summagraphics digitiser and a Prime 300 computer system. From the records the following measurements were made (Fig. 2).

(1) End-diastolic (R wave electrocardiogram) posterior wall thickness (cm).

(2) Peak rate of change of posterior wall thickness in early diastole[8] (cm/s).

(3) Interval from maximum posterior wall thickness to its decline to 20% of peak value, arbitrarily defined as duration of rapid thinning[8] (ms).

(4) Peak rate of increase in left ventricular dimension during early diastole (cm/s).

(5) Duration of increase in left ventricular dimension in early diastole, arbitrarily defined as the time from minimal left ventricular dimension to time of decline in rate to 20% of peak value[7] (ms).

(6) Time intervals (in ms) from minimal left ventricular dimension to the onset of mitral valve opening (measured at cusp separation); and from the first low frequency vibrations of A_2 to mitral valve opening (isovolumic relaxation time).

(7) Change in left ventricular dimension during isovolumic relaxation, expressed as percentage of total dimension change during the cardiac cycle.

STATISTICAL METHODS

Values are quoted as mean ± one standard deviation. Student's t test was used to test differences between variables. The degree of relation between left ventricular function and microvascular complications index and duration of diabetes were estimated with Kendal's rank order correlation coefficient (τ) and Pearson's correlation coefficient (r), respectively.

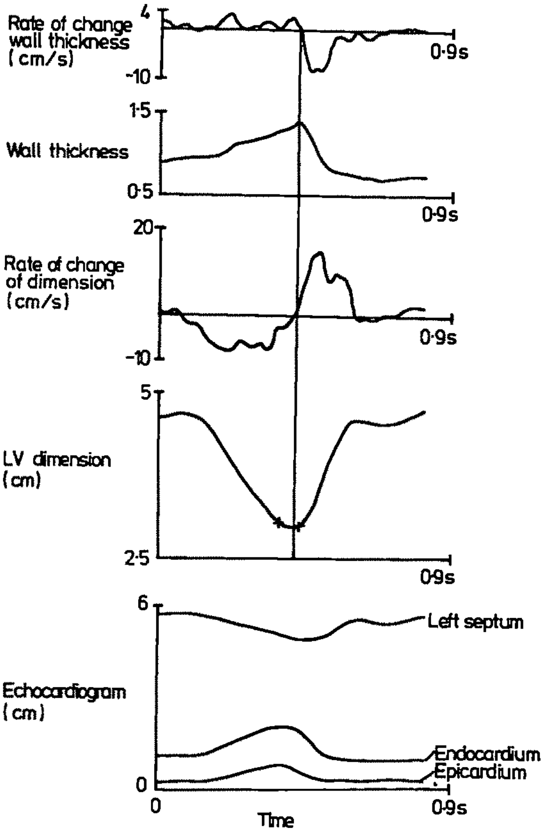

Fig. 2 *Computer output of normal left ventricular (LV) echocardiogram showing from the lowest panel upwards, the digitised data, a continuous plot of left ventricular dimension and its rate of change, and a continuous plot of posterior wall thickness and its rate of change. The two crosses on the dimension trace represent the timing of A_2 and mitral valve opening and the vertical line represents minimal cavity dimension.*

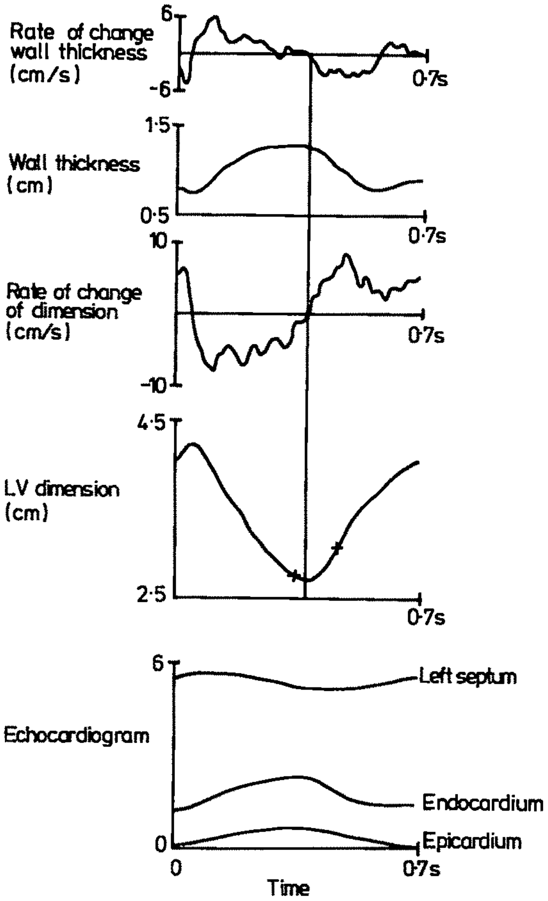

Fig. 3 *Computer output of diabetic with proliferative retinopathy and proteinuria showing delayed mitral valve opening, slow and prolonged filling, and wall thinning.*

Results

(1) COMPARISON OF CONTROL SUBJECTS AND DIABETICS (Table 2)

All diabetics had normal wall thicknesses. Young diabetics with no complications had normal function. The other groups of diabetics had significantly delayed mitral valve opening relative to A_2 ($p<0{\cdot}05$ to $p<0{\cdot}001$) and minimum dimension ($p<0{\cdot}001$). The duration of posterior wall thinning ($p<0{\cdot}001$) and rate of dimension increase ($p<0{\cdot}001$) were significantly abnormal in patients with mild complications, while those with severe complications had abnormalities in all variables of diastolic function measured compared with normal subjects ($p<0{\cdot}001$) (Fig. 2 and 3).

There was a wide scatter of values for the dimension change before mitral valve opening, the mean for diabetics with no, mild, and severe complications being significantly different from normal ($p<0{\cdot}05$, $p<0{\cdot}01$, and $p<0{\cdot}001$, respectively). One hundred and eleven diabetics showed less than a 15% change (3 SD from normal) (mean 4±7%) and the 31 with more than this contributed the majority of the mean change (26±12%). These latter subjects with significant increase in cavity dimension during isovolumic relaxation (incoordinate relaxation) were distributed throughout the diabetic subgroups.

In subjects with coronary artery disease, though the peak rate of dimension increase was moderately reduced from normal ($p<0{\cdot}05$), the major abnormality was delay in mitral valve opening relative to minimum dimension ($p<0{\cdot}001$ vs normal, $p<0{\cdot}01$ to $p<0{\cdot}001$ vs all diabetic subgroups) and the associated dimension change ($p<0{\cdot}001$ vs normal, $p<0{\cdot}01$ vs all

Table 2 *Left ventricular function in control subjects and diabetics*

	No.	*Posterior wall end-diastolic thickness (cm)*	*Peak diastolic rate of change of*		*Duration of*		*Time intervals*		*Dimension change during isovolumic relaxation as % total*
			Wall thickness (cm/s)	*Dimension (cm/s)*	*Rapid thinning (ms)*	*Early diastolic dimension increase (ms)*	*Minimum dimension to MVO (ms)*	*A_2 to MVO (ms)*	
Normal	20	0·8±0·2	11±2	18±4	105±24	166±40	14±3	60±12	3±4
Coronary artery disease	16	0·9±0·2	10±4	14±5‖	115±36	175±47	74±15†	73±25	19±10†
Young diabetics	12	0·8±0·2	11±1	18±2	95±20	153±37	12±3§††	56±7	2±3††
No complications	39	0·8±0·2	10±4	15±5‖	120±41	175±45	32±29†‡	72±21§	8±10‖§
Mild complications	47	0·9±0·2	9±4	13±5†	140±43†	187±47	44±28†††	75±22§	10±8§§§
Severe complications	44	0·9±0·2	7±4†§§	10±5†§§	159±60†§§	226±64†§§	58±23†§§	89±19†	11±9†§§

±, one SD; MVO, mitral valve opening.
Difference from normal: †$p<0\cdot001$; ‡$p<0\cdot005$; §$p<0\cdot01$; ‖$p<0\cdot05$.
Difference between subjects with coronary artery disease and diabetes: ††$p<0\cdot001$; §§$p<0\cdot01$.

Table 3 *Relations of left ventricular function to microvascular complications index (Kendal's rank order correlation)*

	No.	*Peak diastolic rate of change of*		*Duration of*		*Time intervals*		*Dimension change during isovolumic relaxation as % total*
		Wall thickness	*Dimension*	*Rapid thinning*	*Early diastolic dimension increase*	*Minimum dimension to MVO*	*A_2 to MVO*	
All diabetics	142	−0·2†	−0·17‡	0·12‖	0·2†	0·24†	0·23†	0·06¶
Diabetics with a dimension change greater than 3 SD from normal (15%)	31	−0·3§	−0·12¶	0·16¶	0·17¶	0·21‡	0·20‡	0·09¶

Significances: †$p<0\cdot001$; ‡$p<0\cdot005$; §$p<0\cdot01$; ¶NS.

diabetic subgroups). There was, however, only a small prolongation of the isovolumic relaxation time because A_2 and minimum dimension were almost synchronous, compared with the normal interval of 30 to 50 ms. In most diabetics this interval was normal, and delayed mitral valve opening was associated with prolonged isovolumic relaxation, and little dimension change.

(2) RELATIONS TO CLINICAL FEATURES OF DIABETICS

In the total group ($n=142$) there was a close correlation between function and the microvascular complication index. A similar relation was maintained within the subgroup of diabetics with more than 15% dimension change ($n=31$) for peak rate of wall thinning ($p<0\cdot01$), isovolumic relaxation time ($p<0\cdot005$), and interval from minimum dimension to mitral valve opening ($p<0\cdot005$) (Table 3).

In 42 insulin-dependent diabetics diagnosed before the age of 20 years the duration of diabetes was related to peak rate of wall thinning ($p<0\cdot01$), duration of dimension increase ($p<0\cdot01$), isovolumic relaxation time ($p<0\cdot001$), and the interval from minimum dimension to mitral valve opening ($p<0\cdot001$) (Table 4).

Discussion

Computerised interpretation of the M-mode echocardiogram is an excellent way of studying left ventricular diastolic function because of an unequivocal identification of the epi- and endocardial surfaces and mitral valve opening.[7 9]

The timing of aortic valve closure represented by A_2 was normal in healthy subjects and most diabetics. Mitral valve opening was significantly delayed relative to minimum dimension in most diabetics, and this was the result of prolonged isovolumic relaxation. Both were strongly correlated with the microvascular complications index and duration of diabetes[1 6] and, as expected, only young diabetics were normal. Such findings are, however, not specific to diabetes and have been described in other cardiac disorders,[7-11] and are the result of disturbed ventricular relaxation.

In subjects with coronary artery disease and in diabetics with incoordinate relaxation, mitral valve opening was also delayed relative to minimum dimension, but isovolumic relaxation time was only slightly

Table 4 *Relations of left ventricular function to duration of diabetes (Pearson's correlation coefficient)*

	No.	*Peak diastolic rate of change of*		*Duration of*		*Time intervals*		*Dimension change during isovolumic relaxation as % total*
		Wall thickness	*Dimension*	*Rapid thinning*	*Early diastolic dimension increase*	*Minimum dimension to MVO*	*A_2 to MVO*	
Juvenile onset insulin-dependent diabetes	42	−0·4§	−0·3¶	0·2¶	0·44§	0·66†	0·61†	0·24¶

Significances: †$p<0·001$; §$p<0·01$; ¶NS.

prolonged. In this situation it has been shown that though the timing of A_2 is normal, minimum dimension occurs relatively early because of incoordinate systolic wall motion, accompanied by increase in cavity dimension before mitral valve opening, because of incoordinate relaxation.[8-10] Seventy-eight per cent of diabetics and all normal controls showed no significant change of dimension during isovolumic relaxation. There was, however, a wide range of values for dimension change during isovolumic relaxation and 15% (3 SD from normal) arbitrarily defined incoordinate relaxation. This is found in coronary artery disease and other left ventricular diseases and is usually explained by segmental abnormalities of relaxation.[9] Incoordinate relaxation was found in 31 diabetics but there was no trend towards greater dimension change with increasing severity of microvascular complications.

While the incoordination may be the result of microvascular disease with patchy fibrosis impairing regional myocardial function, it is more likely that the cause is asymptomatic but significant coronary artery stenosis, especially as similar abnormalities have been noted in diabetics with angina.[1]

In diabetics with severe complications delayed mitral valve opening was accompanied by prolonged duration and reduced rate of dimension increase, and these abnormalities were closely correlated with the extent of microvascular complications. In diabetics with severe complications the pattern of increase in cavity dimension was similar to that described in mitral[7] and aortic valve stenosis, and hypertrophic cardiomyopathy and severe hypertension.[11] The abnormal filling in mitral stenosis is caused by inflow-tract obstruction, but in aortic stenosis, hypertrophic cardiomyopathy, and hypertension the abnormal filling and relaxation is caused by the altered properties of the hypertrophied ventricle.[8 11] Similarly, in diabetics the pattern of slow and prolonged increase in dimension was not the result of haemodynamic factors, and was totally unlike the asynchronous abnormalities with essentially normal filling in coronary artery disease.

In diabetics wall thickness was normal. In those subjects with severe complications the peak rate of wall thinning was reduced and prolonged in a manner similar to dimension increase; these abnormalities, similar to those found in the hypertrophied myocardium,[8] were correlated to duration of diabetes and microvascular complications. In coronary artery disease rapid wall thinning is normal.[8] Within the subgroup of diabetics with incoordinate relaxation there was a wide range of rates and durations of thinning and increase in dimension, which could also be correlated with the clinical features of diabetes. Therefore, impairment of wall thinning and dimension increase must be the result of abnormal properties of myocardium, which are independent of, and can coexist with, segmental abnormalities of arterial supply.

Diabetics, especially those with severe microvascular complications, have small vessel involvement of the coronary microcirculation analogous to that in the retina and kidney.[12-15] Capillary microaneurysms, basement membrane thickening, and endothelial proliferation have been described in necropsy and biopsy studies. These small vessel abnormalities ultimately induce diffuse myocardial ischaemia, with resultant extracellular fibrosis. Experimental evidence in dogs rendered diabetic with alloxan suggests that myocardial glycoprotein deposition can impair the left ventricular end-diastolic pressure/volume ratio.[13] These pathological changes would disrupt the active processes which determine changes in myocardial properties that are responsible for relaxation and filling.[16] This would readily explain the impaired wall thinning. The role of diffuse ischaemia is uncertain as myocardial cells have a normal structure[13] but may well be important in impairing function.

"Heart failure" and "cardiomyopathy" have been attributed by some authors to diabetes in subjects with recently diagnosed or uncomplicated diabetes or an impaired glucose tolerance test.[15] From this and previous studies,[1 2] it is clear that there is a graded response in left ventricular function to the severity of diabetes; in general only subjects with severe microvascular complications had impaired wall thinning, and heart failure usually only occurred in diabetics with severe complications and was often associated with hypertension.[1] It is, therefore, unlikely that specific diabetic heart disease is responsible for heart failure in subjects with mild diabetes who would not be expected to have coronary microangiopathy, though such patients do have impaired relaxation; this may well explain the increased mortality occurring after myocardial infarction.

The present echocardiographic study shows that in diabetes, though the myocardium is not hypertrophied it has similar properties to those found in myocardial hypertrophy with abnormal relaxation and wall thinning. This supports haemodynamic and histological studies which show that in diabetes there is an intrinsic abnormality of myocardium.

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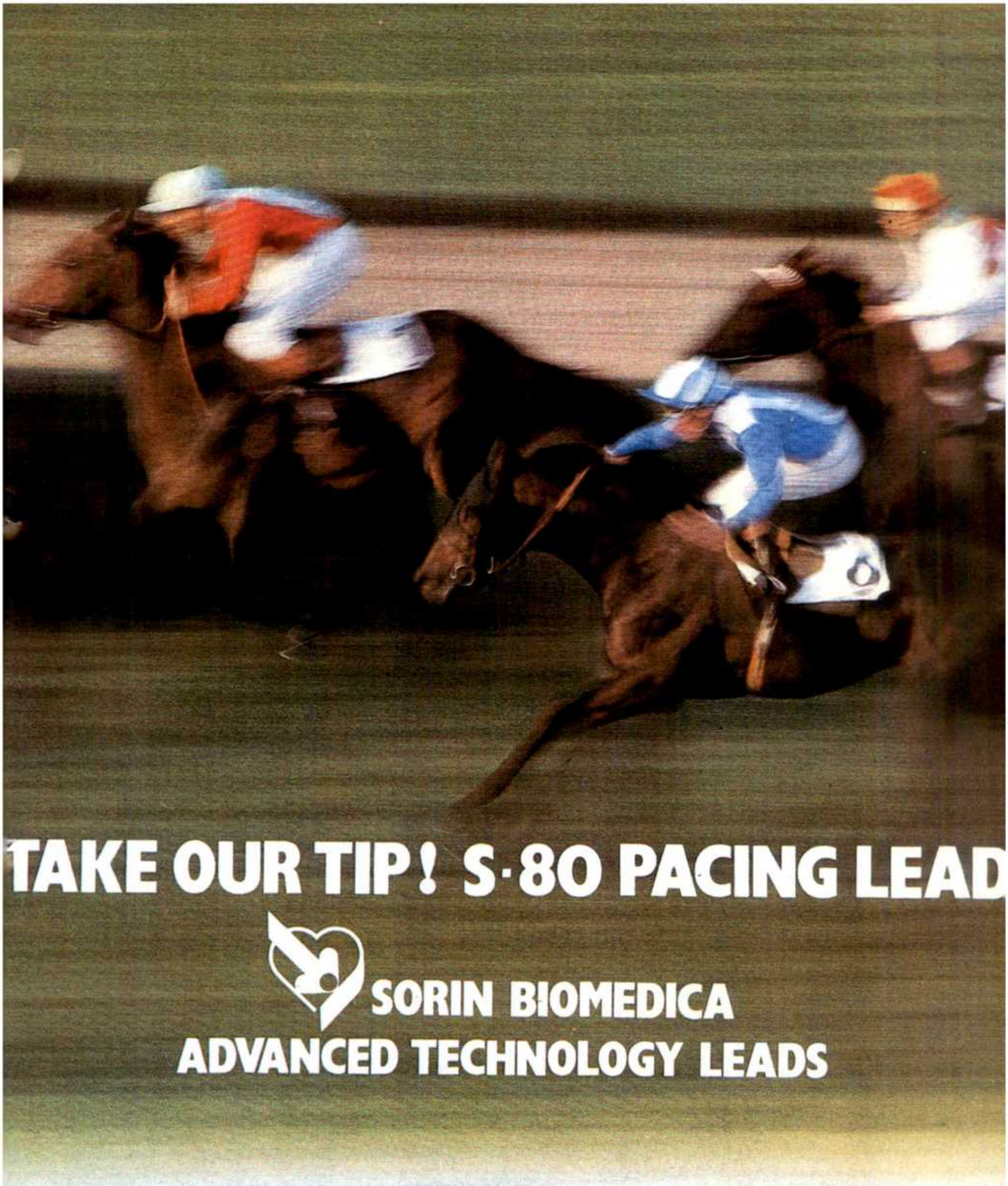

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Detection of atrial septal defect with left-to-right shunt by inferior vena cava contrast echocardiography

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SUMMARY Contrast echocardiography was used before cardiac catheterisation in 37 patients with atrial septal defect and a left-to-right shunt and in 18 patients with a raised right atrial and ventricular pressure to assess the contrast echo effect in the inferior vena cava.

Using two dimensional contrast apical echocardiography we found a negative contrast echo effect within the right atrium in many but not all patients with atrial defect.

Contrast echoes entering the inferior vena cava during presystole or early to mid-diastole were detected in patients with heart disease causing raised right atrial and ventricular pressures and also in all patients with atrial septal defect. No contrast echo effect in the inferior vena cava was detected in 10 normal subjects. The sensitivity of this contrast pattern in the inferior vena cava in diagnosing atrial septal defect was 100%. When other conditions causing raised right atrial pressure were excluded, the specificity and predictive accuracy were 100% for both.

The presystolic contrast echo effect in the inferior vena cava, semiquantitatively graded, correlated with the size of the shunt determined by oximetry.

In 20 patients re-examined after the surgical correction of the atrial septal defect, no presystolic contrast echo effect was detected in the inferior vena cava.

Contrast echocardiography of the inferior vena cava is a valuable and reliable method for diagnosing atrial septal defect with left-to-right shunt.

A dilated right ventricle and paradoxical interventricular septal motion, indicators of right ventricular volume overload, have been used as M-mode echocardiographic criteria for the diagnosis of atrial septal defect.[1-4]

Two dimensional echocardiography has improved the reliability of detection by the direct visualisation of the interatrial communication from the parasternal approach,[4 5] the apical four-chamber view,[6] and the subcostal view.[7 8] Contrast echocardiography has also been used as a sensitive method for detecting right-to-left shunts[9 10]; but is usually considered of little value in patients with left-to-right shunts.[9] Recent investigations, however, have improved its reliability in the latter.[11-13]

The subcostal approach has made it possible to detect contrast echoes entering the inferior vena cava during presystole in patients with an atrial septal defect and a left-to-right shunt and in patients with raised right atrial and ventricular pressure, using the contrast echo technique.[14-16]

The present investigation aimed to test the sensitivity, specificity, and predictive accuracy of presystolic contrast echoes entering the inferior vena cava in patients with atrial septal defect and a left-to-right shunt, comparing them with a group having raised right atrial and right ventricular pressures, and a group of normal subjects.

Patients and methods

We examined 40 consecutive patients (mean age 28±13; range 7 to 54 years) who presented with a clinically suspected atrial septal defect with left-to-right shunt and sinus rhythm. Thirty-seven patients were included in the present study because, from the two dimensional echocardiographic subcostal approach, they showed a dropout of echoes at the level of the interatrial septum, indicating an atrial septal defect.[7 8] Three patients were excluded because

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the septum appeared intact. Eighteen patients (mean age 36±8) with high right atrial and ventricular pressures (eight with pericardial effusion, seven with congestive cardiomyopathy, one with pulmonary stenosis, and two with pulmonary hypertension caused by mitral stenosis, all diagnosed by routine echocardiography) were also studied. Ten normal subjects constituted a third group; all gave informed consent after full explanation.

All patients underwent cardiac catheterisation one to three days after contrast echocardiography. The criteria used to diagnose an atrial septal defect were the presence of a left-to-right shunt on oximetry, the passage of the catheter from the right to the left atrium, and the detection of a jet of contrast passing from the left to the right atrium when the pulmonary angiogram was reviewed in slow motion. We re-examined 20 of the patients with atrial septal defect one to 10 months after its surgical correction.

CONTRAST ECHOCARDIOGRAPHY

Peripheral (left or right antecubital vein) injections of 10 ml 5% glucose solution were given to all patients and normal subjects. A butterfly needle of 1.1 mm in diameter was used. The first injection was intended to test the occurrence of contrast echoes during the two dimensional examination. All subsequent injections in each patient were given by the same operator using the same force, sufficient to obtain a contrast echo effect in the right atrium. All patients and normal subjects were asked to breathe normally during each injection. The echocardiographic approaches used during contrast-producing injections were the two dimensional apical four-chamber views and two dimensional and M-mode subcostal views. One or two injections were given for each view. All contrast injections were continuously recorded without changing the transducer position or gain control during either the two dimensional or M-mode examination.

ECHOCARDIOGRAPHY

A commercially available phased array sector scanner IREX System III and a mechanical sector scanner Aloka SSD 110 S, 2.25 MHz transducer were employed. A complete M-mode echocardiographic examination showed the right ventricular dimensions and the type of the interventricular septal motion (normal, flat, or paradoxical). The two dimensional apical four-chamber view[6] was used to assess the negative contrast echo effect in the right atrium, defined as a contrast-free space along the right side of the interatrial septum and within the right atrium. This was semiquantitatively graded according to the following criteria: absent (−), questionable (+−), weak (+) when a small area of the negative contrast echo effect was present near the right side of the interatrial septum, and strong (++) when a large area of the right atrium was involved in the negative contrast echo effect.

The two dimensional subcostal transverse view[16] was obtained by directing the ultrasonic plane towards the back between the inferior vena cava and pulmonary artery through the right and left atrium and the interatrial septum. This view was used to test the degree of opacification and the direction of contrast echoes entering, or absent from, the inferior vena cava. M-mode echograms of the inferior vena cava were obtained by selecting the single ultrasonic beam from this view and were recorded at a paper speed of 50 or 25 mm/s.

The contrast echo effect was accepted and evaluated when it appeared only in the right atrium or in both the right atrium and the inferior vena cava. In the latter case attention was directed to detecting a real penetration of echoes in the inferior vena cava during presystole, that is before the Q wave of the electrocardiogram on the M-mode echograms. The presystolic contrast echo effect, evaluated on two consecutive inferior vena cava M-mode contrast echograms, was graded according to the following criteria: weak (+) when the contrast echo effect was of low intensity as compared with the intensity of echoes of the other structures and the amount of contrast echo lines, and persisted for one to two cardiac cycles; strong (+ +) when the contrast echo effect was of medium intensity and persisted for three to five cardiac cycles; massive (+++) when the contrast echo effect was of high intensity and persisted for more than five cardiac cycles. These contrast echocardiographic tracings were read blindly and separately by two of us before cardiac catheterisation and, therefore, before the size of the shunt in the patients with atrial septal defect was known.

DATA ANALYSIS

Statistical analysis was performed using the t test. The sensitivity, specificity, and predictive accuracy of the presystolic contrast echo effect in the inferior vena cava to diagnose atrial septal defect were calculated as follows:

True positives (TP)=patients with atrial septal defect and presystolic contrast echo effect in the inferior vena cava.

False negatives (FN)=patients with atrial septal defect and no presystolic contrast echo effect in the inferior vena cava.

True negatives (TN)=patients without atrial septal defect and no presystolic contrast echo effect in the inferior vena cava.

False positives (FP)=patients without atrial septal defect and presystolic contrast echo effect in the inferior vena cava.

$$\text{Sensitivity} = \frac{TP}{TP+FN} \qquad \text{Specificity} = \frac{TN}{TN+FP}$$

$$\text{Predictive accuracy} = \frac{TP}{TP+FP}$$

Results

Cardiac catheterisation confirmed the echo diagnosis in all the patients with raised right atrial and ventricular pressures (range 10 to 28 mmHg) and in 37 patients with two dimensional echo evidence of atrial septal defect. In two patients the latter was a sinus venosus defect and in 35 an ostium secundum defect. The shunt size varied from small to large (range 11% to 88%; Qp/Qs=1·12 to 8·4) (Table) and was left-to-right in all. None of the patients with atrial septal defect had either pulmonary hypertension or raised right atrial and ventricular pressures (Table).

Conventional M-mode echocardiography showed

Table *Haemodynamic, echo, and contrast echocardiographic findings in 37 patients with atrial septal defect*

Catheterisation								*Echo*		*Contrast echo*	
Age (y)	*Qp/Qs*	*L–R shunt*	*LA–RA*		*RVEDP*	*PAP S/D/M*	*PVRI*	*RVD*	*IVS*	*FCV–NC*	*IVC–CE*
			a	*m*							
14	1·12	11%	4	2	8	33/12/17	67	17	N	−	+
36	1·2	13%	1	1	9	15/ 6/12	203	20	N	−	+
10	1·18	15%	2	1	7	30/12/16		15	N	−	+
9	1·37	20%	1	1	6	35/11/18		15	N	−	+
17	1·41	25%	2	1	7	22/10/15	81	18	N	−	+
7	1·51	28%	2	2	7	20/10/15	22	18	N	−	+
23	1·56	30%	3	2	7	28/12/19	76	16	N	−	+
54	1·59	33%	4	4	5	32/10/18	205	25	P	+−	+
17	1·73	42%	3	2	9	21/ 7/13	71	30	N	+	++
23	2·15	53%	3	3	8	28/12/18	35	40	N	+	++
34	2.16	53%	4	2	7	25/10/16	96	25	F	+	++
40	2·21	55%	3	1	7	23/ 7/12	44	35	P	+	++
48	2·33	57%	4	2	9	30/10/20	141	25	N	+	++
49	2·42	59%	3	1	9	30/15/20	165	35	P	++	++
17	2·7	63%	2	2	8	20/10/15	31	30	P	+−	++
49	2·9	66%	4	1	9	33/17/20	169	30	N	+−	++
17	3	67%	1	1	8	23/ 9/15	38	32	N	+	++
33	3·1	68%	3	2	8	17/ 5/ 8	20	30	P	+	++
28	3·1	68%	1	2	8	30/ 7/16	51	40	P	+	++
20	3·14	68%	2	1	7	26/ 9/18	41	30	P	+	++
14	3·18	69%	2	1	8	32/10/17	56	25	P	−	++
45	3·37	69%	2	2	9	26/11/17	81	50	P	+	+++
29	3·33	70%	3	2	8	30/ 9/18	71	25	P	+	++
34	3·36	70%	0	0	9	30/12/18	78	45	P	++	+++
16	3·45	71%	2	1	8	25/12/18	47	30	N	−	++
18	3·5	71%	1	2	5	32/14/23	83	45	P	−	++
36	3·66	73%	3	2	8	25/ 8/15	42	40	F	++	+++
47	4·25	76%	4	2	9	32/13/18	123	38	P	++	+++
24	4·44	77%	2	2	6	27/10/17	24	35	P	+−	++
37	4·5	77%	1	1	5	34/10/20	111	35	P	+	++
27	4·67	77%	3	2	9	28/ 8/13	16	38	P	++	+++
7	4·72	78%	2	1	9	30/12/17	36	42	N	+−	+++
15	4·8	78%	1	0	9	35/12/23	76	35	F	+	+++
50	5	80%	0	0	8	35/14/20	181	40	P	+	+++
24	5·33	81%	2	0	8	30/15/22		40	P	++	+++
32	7·86	86%	1	1	5	20/ 6/11	12	42	P	++	+++
47	8·4	88%	2	2	9	30/10/19	41	44	P	++	+++
8 pts	1·36 ±0·2 p<0·001	21·8 ±8·3 p<0·001	2·3 ±1·2 NS	1·7 ±1·1 NS	7·0 ±1·2 NS			18·0 ±3·3 p<0·001			+
18 pts	2·96 ±0·7 p<0·001	64·1 ±9·2 p<0·001	2·4 ±1·1 NS	1·6 ±0·6 NS	7·6 ±1·3 NS			32·1 ±5·7 p<0·01			++
11 pts	5·03 ±1·6	77·8 ±5·9	1·8 ±1·3	1·1 ±1	8·3 ±1·2			41·2 ±4·1			+++

Abbreviations: Qp/Qs, pulmonary to systemic flow ratio; L–R, left-to-right; LA–RA, left atrial–right atrial pressure gradient (mmHg) measured at "a" wave (a) or the mean (m); RVEDP, right ventricular end-diastolic pressure (mmHg); PAP, pulmonary artery pressure (mmHg); S, systole; D, diastole; M, mean; PVRI, pulmonary vascular resistance index (mean PAP—pulmonary wedge pressure)/cardiac index (1 resistance unit=80 dynes s cm^{-5}); RVD, right ventricular dimension in mm; IVS, interventricular septal motion (P, paradoxical; F, flat; N, normal); FCV–NC, negative contrast echo from apical four chamber view; IVC–CE, presystolic contrast echo effect in the inferior vena cava; −, absent; +−, questionable; +, weak; ++, strong; +++, massive; NS, not significant; pts, patients.

the typical combination of a dilated right ventricle and abnormal interventricular septal motion in 20 of our 37 patients. Normal interventricular septal motion was recorded in 14 patients, and the combination of a normal right ventricle and normal interventricular septal motion was found in seven patients with the lowest values of shunt (Table).

CONTRAST ECHOCARDIOGRAPHY

All injections performed in an individual patient produced a similar contrast echo effect, which in the majority of cases was evaluated identically by the two observers. In five patients with atrial septal defect the findings on the apical view were considered questionable because of different interpretation of the two observers.

In none of the normal subjects were contrast echoes entering the inferior vena cava detected. In all the patients and normal subjects, however, a satisfactory opacification of the right atrium and ventricle was obtained.

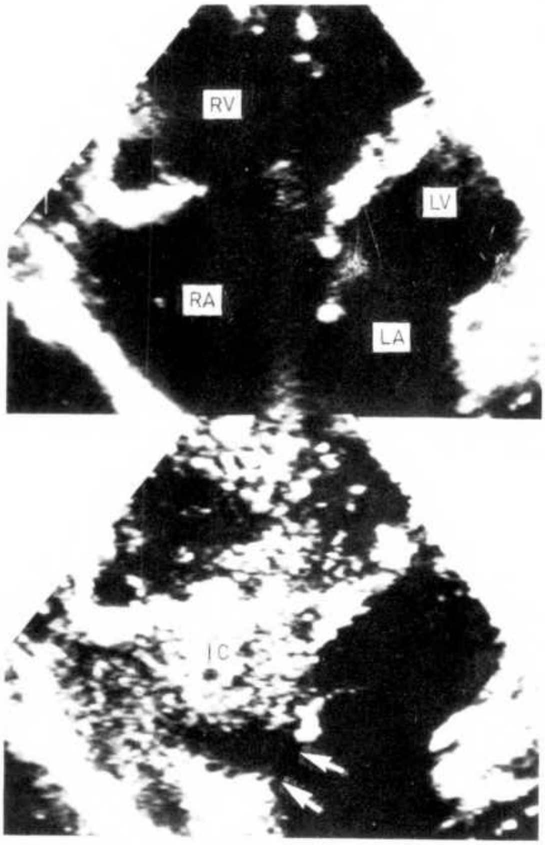

Fig. 1 *Two dimensional apical four-chamber view in patient with atrial septal defect just before (top) and during (bottom) contrast echocardiography. Arrows indicate a weak negative contrast echo effect. RA, right atrium; RV, right ventricle; LA, left atrium; LV, left ventricle; C, contrast echoes.*

From the apical approach a negative contrast echo effect in the right atrium of the patients with atrial septal defect was absent in 10, questionable in five, weak in 14, and strong in eight (Table; Fig. 1). No correlation was found between the graded negative contrast echo effect and the size of the shunt (Table).

In all patients with atrial septal defect and in 10 patients with a raised right ventricular pressure, from the subcostal transverse view, a to-and-fro motion of contrast echoes between the right atrium and the inferior vena cava with a direction perpendicular to the incidence of the ultrasonic place was found (Fig. 2). In these patients contrast echoes were seen entering the inferior vena cava during early diastole and/or presystole, that is after the T wave and/or before the Q wave of the electrocardiogram, as seen in the M-mode tracings (Fig. 3A, B, C). In some of the patients presystolic or early diastolic contrast echoes were detected which were synchronous with the "a" wave or after the "v" wave of either the inferior vena cava echocardiogram or the jugular pulse, when it was able to be recorded (Fig. 4). The sensitivity, specificity, and predictive accuracy of the presystolic contrast echo effect in the inferior vena cava for diagnosing atrial septal defect with left-to-right shunt were 100%, 50%, and 77%, respectively. In all the patients with a raised right ventricular pressure the M-mode and/or two dimensional conventional echocardiographic examinations were sufficient to establish the main cardiac diagram. When these patients were excluded, the specificity and predictive accuracy of the presystolic contrast pattern in diagnosing atrial septal defect were 100% for both.

In eight patients with congestive cardiomyopathy or pericardial effusion with the lowest values of right ventricular pressure, false penetration of contrast echoes in the inferior vena cava was identified if echoes appeared to have a to-and-fro motion towards the transducer, if they were identified outside the inferior vena cava and, finally, if they disappeared when the single beam for the M-mode echo of the inferior vena cava was selected further from the right atrium, or when the transducer was angulated towards the inferior vena cava (Fig. 5).

Using the same procedure for all patients with atrial septal defect, the same opacification of the right atrium was obtained in all, though different degrees of opacification of the inferior vena cava were observed. In these patients the graded contrast echo effect in the inferior vena cava was weak in eight, strong in 18, and massive in 11 (Table). At catheterisation the values of the oximetric shunt were found to be directly related to the graded contrast echo effect (Table). In 20 post-

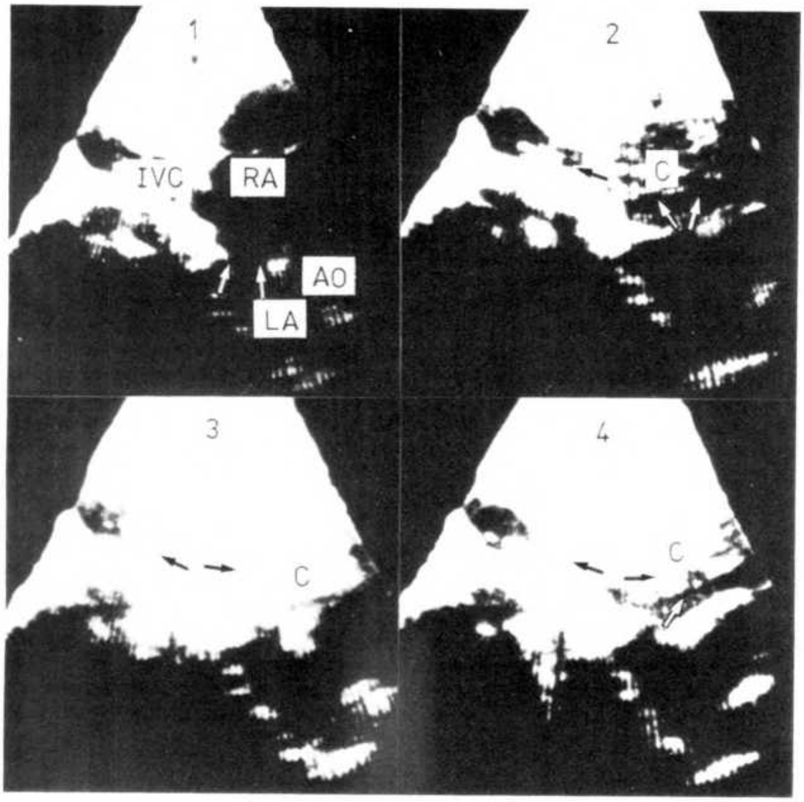

Fig. 2 *Two dimensional subcostal transverse view. Subsequent frames during contrast injection in patient with atrial septal defect. Arrows in panel 1 indicate the dropout of echoes between the right (RA) and left (LA) atrium. Contrast echoes (C) enter the inferior vena cava (IVC) from the right atrium with a to-and-fro motion (black arrows) perpendicular to the incidence of the ultrasonic plane. White arrows indicate non-contrast-containing blood coming from the left atrium.*

operative patients no contrast echoes were found to enter the inferior vena cava during presystole and the opacification of the right atrium and ventricle was normal. The absence of presystolic contrast echoes in the inferior vena cava after surgery is well documented in Fig. 6. In this case, contrast 1 (presystole) and contrast 2 (late systole) in panel A were attributed to an atrial septal defect and tricuspid regurgitation caused by tricuspid valve prolapse, respectively, as shown by cardiac catheterisation. After surgical correction of the septal defect no contrast echoes were detected in the inferior vena cava during presystole, whereas only contrast 2 was present (arrows in panel B) and attributed to the persistence of tricuspid regurgitation.

Discussion

M-mode echocardiograms are not specific and sensitive enough to prove the presence of atrial septal defect with left-to-right shunt.[1-3] In fact, these findings may be absent in patients with small atrial septal defects and small left-to-right shunts, and it is more frequent to record a normal M-mode echocardiogram or a normal interventricular septal motion even when the shunt is large[5] (Table). Using two dimensional contrast echocardiography some authors[11-13] noticed a negative contrast echo effect in the right atrium, that is a contrast-free space along the right side of the interatrial septum caused by the non-contrast-containing blood passing from left to right across the defect (Fig. 1). This effect is enhanced during the Valsalva manoeuvre,[11] but not in all patients with atrial defect and left-to-right shunt was it detected clearly (Table). The reliability of this technique in diagnosing the defect depends upon many factors, such as poor sound transmission characteristics, too few contrast echoes,[13] and the position of the transducer.

We have previously observed presystolic contrast echoes entering the inferior vena cava in patients with atrial septal defect and a dominant left-to-right shunt, and attributed the contrast echo feature to the flow directed from left to right and towards the inferior vena cava.[16]

In the present investigation this pattern had a sensitivity of 100% but a low specificity and predictive accuracy in diagnosing atrial defect. This is because other conditions determining raised right atrial and ventricular pressure appeared to have a presystolic

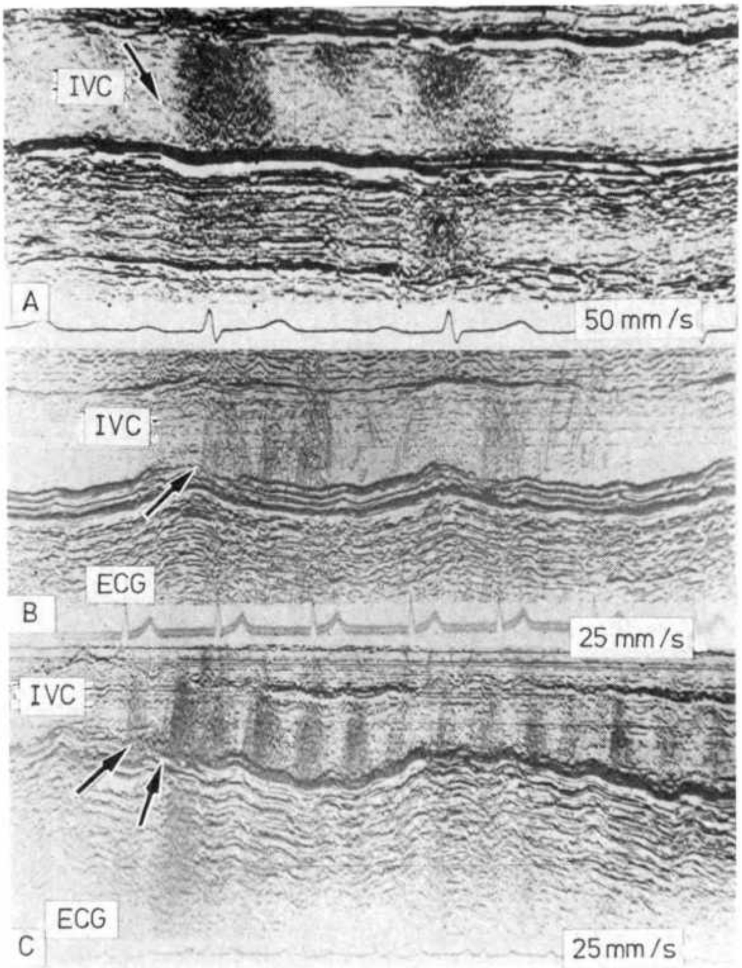

Fig. 3 *M-mode inferior vena cava (IVC) contrast echocardiograms in atrial septal defect and left-to-right (L–R) shunt. Panel A, patient with small L–R shunt. Arrow indicates the presystolic appearance of contrast echoes persisting for two cardiac cycles. Notice the absence of contrast during the third beat. Panel B, patient with L–R shunt of medium size. Arrow indicates the presystolic appearance of contrast lines persisting for four cardiac cycles. Panel C, patient with large L–R shunt. Arrows indicate the diastolic appearance of contrast echoes persisting for more than five cardiac cycles.*

contrast echo effect. When these were excluded by the initial M-mode and two dimensional echo scan the specificity and predictive accuracy increased significantly and the presence of the defect was proved in 100% of the cases. Other conditions that could affect this echo pattern include the cardiac rhythm, inspiration, and false entry of contrast echoes in the inferior vena cava. The timing of appearance of contrast echoes must first be identified. This is easy when contrast echoes appear during presystole, that is just before the Q wave of the electrocardiogram. The diastolic appearance is sometimes difficult to define, especially when the T wave of the electrocardiogram is not clearly inscribed. In both cases, however, the "a" and "v" waves of either the inferior vena cava or the jugular pulse may help to define clearly the timing of the appearance of contrast[17] (Fig. 4). As previously reported, neither atrial fibrillation nor inspiration modify the time relation between the cardiac cycle and the entry of contrast echoes into the inferior vena cava.[16 18] In the present series, however, all patients with atrial septal defect presented with sinus rhythm, and no difference was observed in the results during either regular breathing or held respiration. Furthermore, if the transducer is abnormally positioned it may be possible to detect contrast echoes recirculating into the right atrium, superimposed on the inferior vena cava, and erroneously localised inside it. This false entry may be identified by altering the angle of the transducer and reviewing the two dimensional recordings in slow motion or frame by frame (Fig. 5).

On the other hand, despite all these limitations, the reliability of the presystolic contrast echo effect in the inferior vena cava for the diagnosis of atrial septal defect with left-to-right shunt is also supported in this study by the fact that this effect is absent in patients

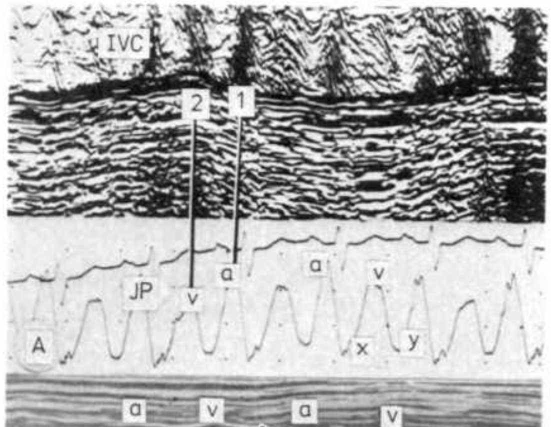

Fig. 4 *Contrast M-mode echograms of the inferior vena cava (IVC). Panel A, patient with tricuspid regurgitation and atrial septal defect. Presystolic (1) and systolic (2) contrast echoes are synchronous with the "a" and "v" waves of the jugular pulse (JP), respectively. Panel B, patient with atrial septal defect. Contrast lines enter the inferior vena cava after both the T wave of the electrocardiogram and peak "v" wave of the inferior vena cava (second and third arrow). The first arrow indicates presystolic contrast lines synchronous with the "a" wave. Panel C, patient with tricuspid regurgitation and pulmonary hypertension caused by severe mitral stenosis. Contrast lines (arrow) are synchronous with the peak "v" wave of the inferior vena cava. Contrast synchronous with the "a" wave is also visible.*

after operation (Fig. 6). In order to test any possible relation between the oximetric size of the shunt and the graded appearance of contrast echoes in the inferior vena cava we divided the patients into three groups according to whether they presented a weak, strong, or massive contrast echo effect. These groups bore a significant relation to the size of shunt but not to the mean left-to-right atrial pressure gradient or the right ventricular pressure (Table).

It is possible that this effect is the result of the flow directed from left to right towards the inferior vena cava, during diastole and, particularly, during presystole when the contraction of both atria occurs.[16] This is in agreement with Doppler echo studies on patients with atrial septal defect previously reported.[19–21] Moreover, since the patients with low shunts on oximetry had weak contrast echo effects, whereas those with high shunts showed massive ones, it is inferred that the graded appearance of contrast echoes in the inferior vena cava be related to the left-to-right oximetric shunt and, therefore, to the amount of flow. The ability of the techinque to grade and anticipate the size of the shunt, even if semiquantitatively, may depend upon many factors such as the force of injection, the velocity of blood flow, and respiratory events, which may modify the intensity and the amount of contrast echoes.[16] In the present study, however, all patients either breathed normally or held their breath, all injections were performed by the same operator, and in individual patients contrast echo effects were seen to be reproducible. In conclusion, the presystolic appearance of contrast echoes in the inferior vena cava is a reliable and useful method of proving the presence of atrial septal defect with left-to-right shunt, particularly in those patients suspected of having the defect but with normal findings on conventional echocardiography.

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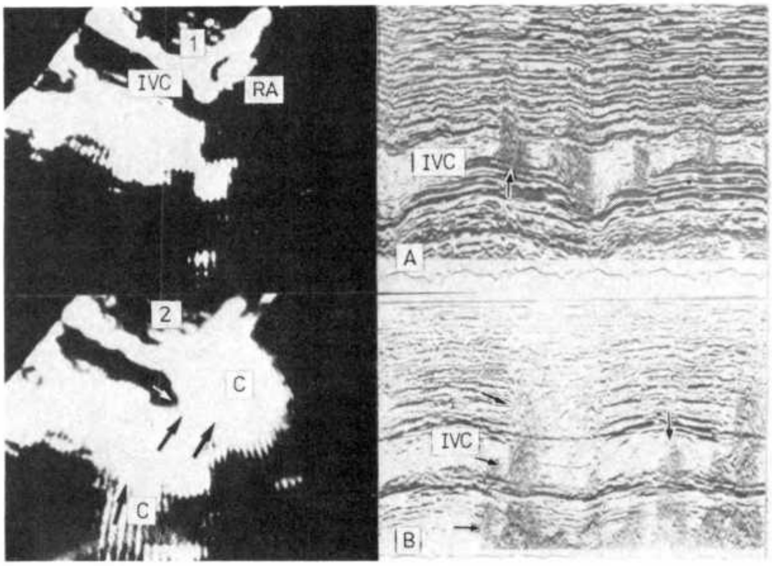

Fig. 5 *On the left, sequential frames of two dimensional contrast echocardiogram in a case of false entry of contrast echoes (C) in the inferior vena cava (IVC). Contrast echoes are identified near the entry of the inferior vena cava, outside it and within the right atrium (RA) at the same time, with a to-and-fro motion towards the transducer (black arrows) and superimposed on the inferior vena cava (compared with Fig. 2). White arrow indicates blood without contrast material coming from the inferior vena cava. On the right, inferior vena cava (IVC) contrast M-mode echogram. Panel A, true entry (patient with atrial septal defect) of contrast echoes in the inferior vena cava, when the single beam was selected further from the right atrium. Arrow indicates presystolic contrast lines in the inferior vena cava. Panel B, false entry of contrast echoes in the inferior vena cava. Arrows indicate contrast echoes superimposed on the inferior vena cava and outside of it. In this case no contrast echoes were detected inside the inferior vena cava when the beam was selected further from the right atrium.*

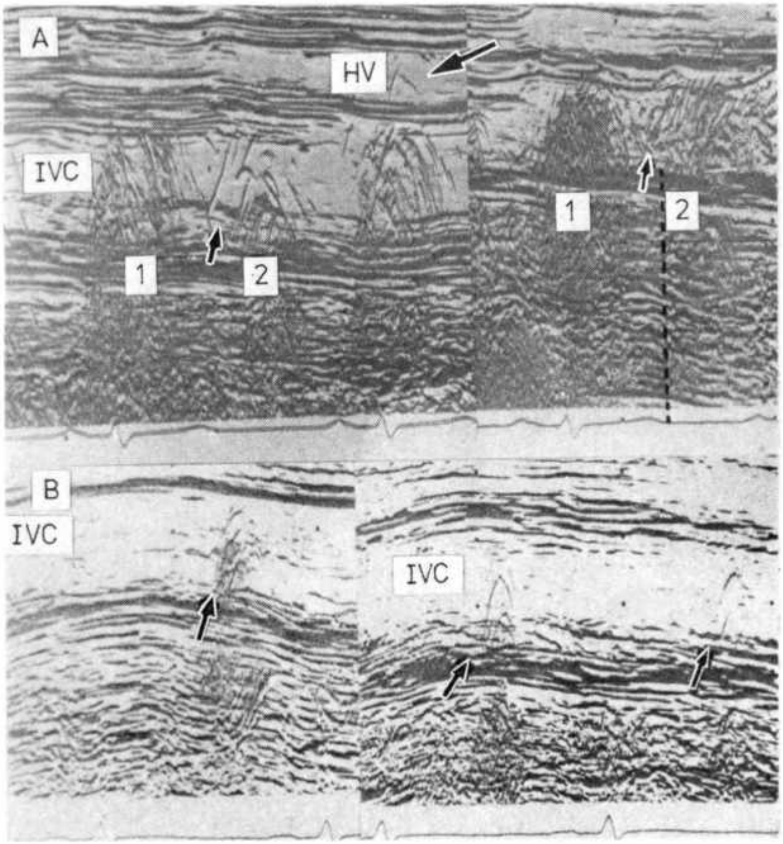

Fig. 6 *M-mode contrast echogram of the inferior vena cava in case of tricuspid regurgitation caused by late systolic prolapse and atrial septal defect. Panel A, contrast echoes enter the inferior vena cava during presystole (1) and late systole (arrows in 2). Upper arrow indicates contrast lines in the hepatic vein (HV). Panel B, same patient after surgical correction of the septal defect. No presystolic echoes are seen. Arrows indicate the persistence of contrast echo lines 2 seen in panel A.*

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Echocardiographic abnormalities of tricuspid valve motion in pulmonary embolism

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SUMMARY Echocardiographic findings in five patients with pulmonary embolism were studied. Tricuspid echocardiograms showed abnormalities in valve motion, that is a monophasic triangular wave during diastole in all the patients as well as an increased dimension of the right ventricle. An "a" dip of the pulmonary valve echocardiogram was also recognised in all five. Later tricuspid echocardiograms regained the normal M-shaped configuration.

The monophasic triangular pattern of the tricuspid valve during diastole may be related to the shorter duration of tricuspid valve opening compared with that of the mitral valve. Tachycardia cannot explain this difference between tricuspid and mitral valve motion, which seems to be caused by a prolonged isovolumic relaxation time of the right ventricle resulting in a delayed opening of the tricuspid valve. These results were obtained by comparing these data with those of control subjects and patients with chronic right ventricular overloading resulting from atrial septal defect.

The most common haemodynamic derangement in patients with acute or subacute pulmonary embolism is pulmonary hypertension in frequent association with right heart failure. It has been suggested that acute depression of contractile force, which a previously normal right ventricle can generate, ensues. Echocardiography is a useful non-invasive method to evaluate cardiac function; we used it to assess right ventricular function sequentially in five patients with pulmonary embolism. There is little information on echocardiographic findings in this disorder,[1–3] and our findings have not been previously described. Attempts were made to ascertain the possible mechanisms of the abnormal configuration of tricuspid valve motion during diastole. These data were compared with those of normal subjects and patients with chronic right ventricular overload resulting from atrial septal defect.

Subjects and methods

The diagnosis of pulmonary embolism was confirmed by pulmonary perfusion scan and/or pulmonary arteriogram in all five patients. One of them had a second attack. The instrument used in this study was a commercially available ultrasonoscope type SSD 90 or 110 (Aloka) or Type OIA (Toshiba) with a 0·5 in, 2·25 or 3·5 MHz transducer focused at 7 cm. An attempt was made in each patient to record echoes from all cardiac valves, and the ventricular septum and walls. The patients were examined in the supine position and the recording was made during held mid-expiration. The echocardiograms were recorded at a paper speed of 50 mm/s simultaneously with lead II of the electrocardiogram and the phonocardiogram.

The isovolumic relaxation time of the right ventricle (P2-To interval) was measured from the closure of the pulmonary valve identified by the pulmonary component of the second sound of the phonocardiogram (P2) to the opening of tricuspid valve (To) judged from the echocardiogram. The duration of the tricuspid valve opening (To-Tc interval) was determined by the echocardiogram and the systolic duration of the right ventricle was measured from the closure of the tricuspid valve (Tc) to that of the pulmonary valve (Tc-P2). We were able to identify the closure of the pulmonary valve definitely from a combination of the phonocardiogram and the echocardiogram. In our study P2 was used for the measurement, since the closure of the pulmonary valve was not always recorded on the echocardiogram.

For comparison with these data, six healthy sub-

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jects with no heart disease and 24 patients with atrial septal defect were studied. Twelve of the 24 had an uncomplicated atrial septal defect with predominant volume overloading of the right ventricle and 12 had a complicated atrial septal defect with pulmonary hypertension (mean pulmonary artery pressures greater than 30 mmHg) or combined volume and pressure overloading of the right ventricle. Tracings of control subjects were obtained at a heart rate varied by ergometer exercise performed supine.

STATISTICAL ANALYSIS

The difference between means was assessed for statistical significance by Student's t test. A p value of less than 0·05 was considered to be significant. Regression analysis and Peasson's correlation coefficient were obtained using standard statistical methods.

Case report

A 34-year-old man was admitted to Hyogo College of Medicine Hospital on 18 November 1977 because of severe dyspnoea and cyanosis. He had undergone thrombophlebotomy of the right femoral vein five years previously when he had had an episode of acute pulmonary embolism. On the day of admission, blood pressure was 124/100 mmHg, pulse rate 120/min, and respiration rate 30/min. The lung fields were clear to auscultation and percussion. Arterial blood gas analysis revealed a Po_2 of 54 mmHg, a Pco_2 of 26·1 mmHg, and a pH of 7·466 while he was breathing room air. A chest *x*-ray film showed dilatation of the pulmonary artery stem, clear lung fields, and normal heart size. The electrocardiogram showed S waves in lead I, Q waves in lead III, and inverted T waves in V1–4. Serial enzymes showed a transient rise in serum lactic dehydrogenase up to 640 IU without changes in serum aspartate transaminase, pyruvate transaminase, and creatine kinase. A pulmonary perfusion scan disclosed large perfusion defects in both lower fields. After the start of anticoagulation treatment with heparin and warfarin, his condition improved steadily and symptoms went. Sequential echocardiographic examinations were performed, showing the striking abnormalities in tricuspid valve echocardiogram shown in Fig. 1. Tricuspid valve echocardiogram, taken on the 10th day after the embolism (Fig. 1A) showed a monophasic triangular wave during diastole which has not been described previously. The tricuspid echocardiogram taken 40 days later (Fig. 1B) showed persistence of the monophasic triangular configuration during diastole, but the tricuspid valve showed a slow upward motion during early diastole. Ten months later the tricuspid valve echocardiogram (Fig. 1C) showed the notched diastolic configuration pattern in which probably E and A points occur simultaneously, and the interruption of tricuspid closure commonly called a B-B′ step. Eighteen months later, the tricuspid valve echocardiogram (Fig. 1D) showed the M-shaped configuration during diastole and lengthening of the AC interval. Fig. 1A also illustrates the mitral valve echocardiogram taken immediately after admission, which showed the M-shaped appearance during diastole, and it was noticed that the duration of mitral valve opening was longer than that of tricuspid valve opening.

ECHOCARDIOGRAPHIC FINDINGS IN PULMONARY EMBOLISM

The echocardiographic findings and right-sided catheterisation data in five patients with pulmonary embolism are summarised in Table 1. The characteristic configuration of the monophasic triangular wave of the tricuspid valve during diastole was observed from 12 hours to 40 days after the attack in all the cases. The dimension of the right ventricle measured from 12 hours to 20 days after the attack increased to more than 30 mm in all cases. The "a" dip of the pulmonary valve echocardiogram was found in all five cases.

The isovolumic relaxation time of the right ventricle in normal subjects varied within a small range from 20 to 30 ms (24±4 ms, mean±SD) at heart rates between 50 and 134 per minute, as shown in Fig. 2. The isovolumic relaxation time was found to correlate with the heart rate ($r=-0·715$, $p<0·05$). Thus, the correction for heart rate is required for the isovolumic relaxation time (Table 2). The mean isovolumic relaxation time for the group with uncomplicated atrial septal defect was 30·9 ms and was slightly prolonged. The isovolumic relaxation time was significantly prolonged in the groups with pulmonary embolism and a complicated atrial septal defect. The To-Tc interval was inversely related to the heart rate ($r=-0·924$, $p<0·05$) (Fig. 3). This value corrected for heart rate for groups with atrial septal defect and pulmonary embolism was significantly shortened as compared with that for control groups (Table 2). The Q-Tc interval was found not to correlate with the heart rate ($r=-0·06$, $p>0·05$) (Fig. 4), and it was not different in groups with pulmonary embolism compared with that for the control group, as shown in Table 2. This indicates that the timing of the tricuspid valve closure for pulmonary embolism was not altered. The $Q\text{-}P_2$ interval was inversely related to the heart rate ($r=-0·959$) (Fig. 5), and this value for pulmonary embolism was similar to that for the control group (Table 2). This observation shows that the opening of the tricuspid valve was delayed while timing of the pulmonary valve closure was not significantly altered.

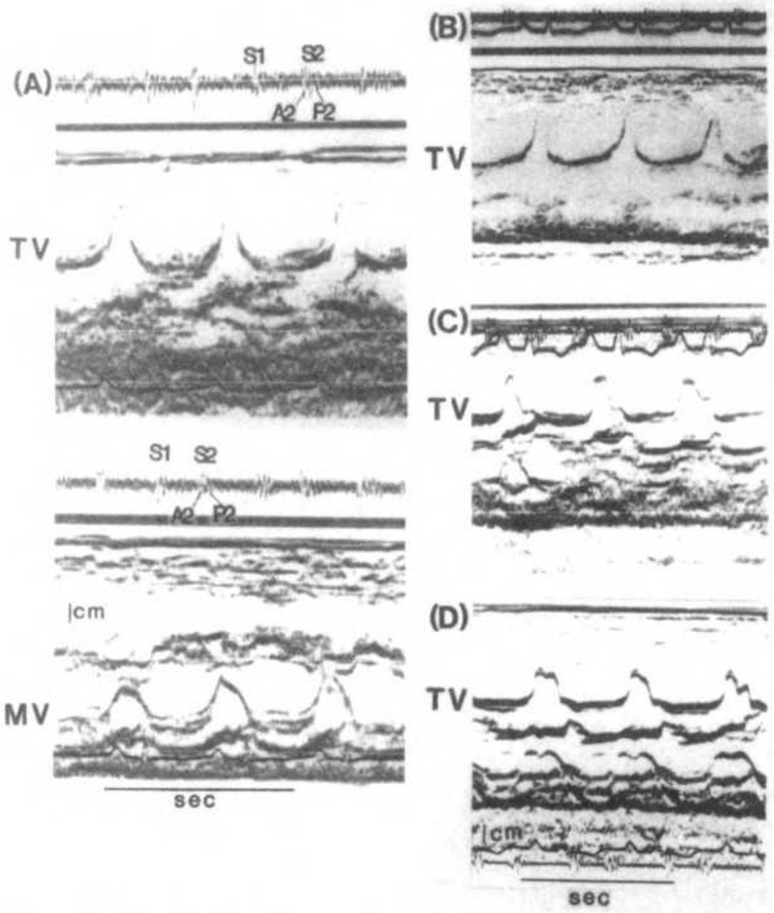

Fig. 1 *Tracing from a patient with pulmonary embolism. (A) Recorded 10 days afterwards. The tricuspid valve echocardiogram showed the monophasic triangular wave during the diastolic phase. The mitral valve echocardiogram was recorded at the same time as the tricuspid valve, and the opening period of the mitral valve was longer than that of the tricuspid valve. (B) Recorded 40 days after the attack showed the tricuspid valve moving slowly and anteriorly during early diastolic phase. (C) Recorded 10 months after the attack showed the BB' step. (D) Recorded 18 months after the attack and showed the M-shaped pattern. TV, tricuspid valve; MV, mitral valve; S1, first heart sound; S2, second heart sound; A2, second heart sound of aortic valve; P2, second sound of pulmonary valve.*

Discussion

Several echocardiographic studies on pulmonary embolism have described the increased dimension of the right ventricle and paradoxical motion of interventricular septum.[1-3] To our knowledge, this is the first demonstration of the striking abnormalities of tricuspid valve motion during diastole, that is the monophasic triangular wave produced by a single opening-closing movement instead of the initial early diastolic opening, mid-diastolic closure, and atrial reopening. These abnormal findings were confirmed in all the five patients by repeated echocardiographic examination performed from 12 hours to 40 days after pulmonary embolism.

It was suggested that this peculiar wave is produced by the fusion of E and A points as a result of tachycardia which is known to produce the monophasic trian-

Table 1 *Echocardiographic and haemodynamic findings*

Case No.	*Age (y) and sex*	*Time after onset*	*Echocardiographic findings*						*Haemodynamics (mmHg)*
			Tricuspid valve echo			*Pulmonary valve echo*			
			Monophasic triangular wave	*M-shaped pattern*	*RVDd (mm)*	*"a" dip (mm)*	*b-c (mm/s)*	*e-f (mm/s)*	
1	34M	10 d	+		38	3	360	2	
		40 d	+		45	3	380	4·5	
		10 mth			45	1·5	435	9	
		18 mth		+	45	0	520	0	
2	28F	24 h	+		40	7	214	36	RV:40/14 RA:a=14, (mean=11)
		40 d		+	30	3	450	34	
3	28M	12 h	+		30	3	250	8·3	PA:60/35(45) RV:60/8 RA(14)
		19 d		+	25	0	260	0	PA:34/18(24) RV:34/13 RA(13)
4	26M	20 d	+		30	2	400	15	PA:63/24(35) RV:63/7 RA(6)
		40 d		+	18	4	196	12	PA:29/8(16) RV:28/6 RA(5)
5	49F	12 h	+		40	1	280	11	

RVDd, right ventricular end-diastolic dimension; RV, right ventricle; RA, right atrium; PA, pulmonary artery; +, present.

gular wave of the mitral valve by shortening diastole.[4] In fact, one factor that obviously influences the appearance of the atrioventricular valve echo is the heart rate. When the heart rate is faster and diastole shorter, there will be no plateau between early and late diastolic filling, and at times the E and A points may even merge with each other. This explanation is unlikely in these cases, since the abnormalities of tricuspid valve motion present a striking contrast to the normal appearance of the mitral valve motion in configuration and diastolic duration recorded simultaneously in the same patient, as shown in Fig. 1 and Table 3. The duration of the tricuspid valve opening is significantly shorter than that of the mitral valve. These observations suggest that these abnormalities cannot be accounted for only by the tachycardia. Attempts to define the mechanism of abnormalities of tricuspid valve motion were performed by analysing its relation to cardiac events. The isovolumic relaxation time of the right ventricle was found to be nearly constant in normal subjects over a broad range of heart rates, and at any given rate the duration of this interval was significantly prolonged in the groups with pulmonary embolism and complicated atrial septal defect. This prolongation in these disorders could be related to an increase in pulmonary artery pressure[5 6] or an impairment in contractility of the right ventricle[7] but, though pulmonary hypertension secondary to pulmonary embolism was either similar or less severe than that found in the group with atrial septal defect, the isovolumic relaxation time of the right ventricle was more prolonged in the former group (Tables 1 and 2).

This observation indicates that the timing of tricuspid valve opening is delayed in these situations. Thus, the delayed opening of the tricuspid valve is in part responsible for the abnormal configuration of the tricuspid valve in diastole. In this study the Q-P2 interval was not prolonged in the group with pulmonary embolism, indicating that the timing of pulmonary closure is not delayed. The Q-Tc interval was not altered in the groups with pulmonary embolism, demonstrating normal closure of the tricuspid valve.

The reduced To-Tc interval was observed not only in the group with pulmonary embolism but also in that with atrial septal defect, though the monophasic triangular wave of tricuspid valve motion in diastole was recorded in the former, but not in the latter. The peculiar pattern shown on the echocardiogram seems to be related to the significant differences between the two groups in the prolongation of the isovolumic relaxation time resulting in delayed tricuspid valve opening and shortened duration of tricuspid valve opening, as shown in Table 2. The separation of the patients with pulmonary embolism into two subgroups, that is those with and those without the monophasic triangular wave, presumably depends on the same reasons. The normal M-shaped configuration of tricuspid valve motion in diastole was regained later. This seemed to be related to the reduction in heart rate and moderate improvement in the prolonged isovolumic relaxation time (Fig. 2).

The pulmonary valve echocardiogram showed the deep "a" dip in five cases, thought to be related to severe right heart failure.[8] In previous echocardiographic studies on pulmonary embolism, only the increased dimension of the right ventricle and the paradoxical motion of the interventricular septum have been observed.[1] In our cases, the increased dimension of the right ventricle was shown in all the

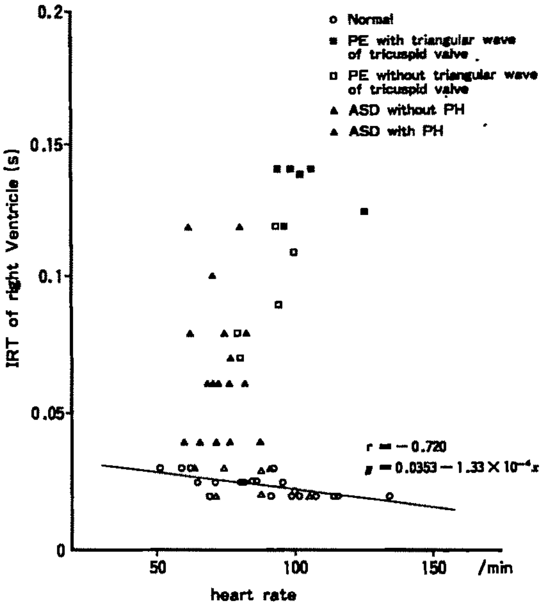

Fig. 2 *The isovolumic relaxation time (IRT) plotted against heart rate for the four groups. PE, pulmonary embolism; ASD, atrial septal defect; PH, pulmonary hypertension. Regression line and correlation coefficient shown are for the control group.*

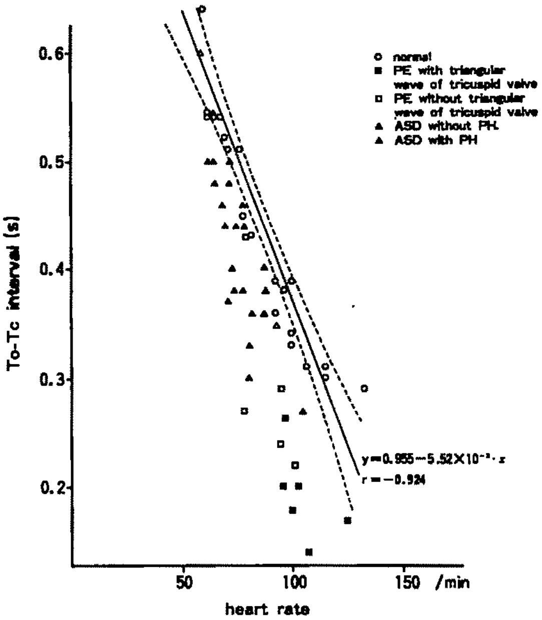

Fig. 3 *The To-Tc interval plotted against heart rate for the four groups. Abbreviations in the following figures as in Fig. 2. Regression line and correlation coefficient shown are for the control group.*

Table 2 *Non-invasive measurement of cardiac interval data*

		HR	*IRT of right ventricle (%)*	*Q-P2 interval (%)*	*To-Tc interval (%)*	*Q-Tc interval (s)*	*Mean PAP*	*Qp/Qs*
Healthy subjects (n=20)		87·1 ±20·8	100·2 ±11·2	101·1 ±7·4	101·0 ±14·1	0·07 ±0·01		
Atrial septal defect	Without PH n=12	79·1 ±12·8	123·8* ±36·1	106·5 ±6·5	90·9* ±8·7	0·075 ±0·009	17·0 ±3·1	3·0 ±1·3
	With PH n=12	74·0* ±6·0	310·6* ±83·5	107·5* ±5·3	78·3* ±8·3	0·073 ±0·009	43·0 ±14·3	2·0 ±0·9
Pulmonary embolism	With triangular wave n=6	104* ±10·1	620·9* ±92·8	96·8 ±6·3	53·1* ±7·4	0·064 ±0·018		
	Without triangular wave n=5	89 ±8·8	407·9* ±92·8	100.1 ±8·2	66·8* ±12·5	0·077 ±0·01		

PAP, pulmonary arterial pressure; PH, pulmonary hypertension; Qp/Qs, the ratio pulmonary and systemic blood flow.
Other abbreviations as in text.
Asterisks (*) indicate significant differences from the corresponding values of healthy subjects or between groups.
The regression equations used to calculate the cardiac intervals.
IRT, $0{\cdot}0353-1{\cdot}33\times10^{-4}.X$ (X=heart rate). $Q\text{-}P2=0{\cdot}535-1{\cdot}86\times10^{-3}.X$ $To\text{-}Tc=0{\cdot}925-5{\cdot}52\times10^{-3}.X$
The calculated value for each interval was expressed as $\frac{\text{measured value}}{\text{predicted values}}\times100.(\%)$.

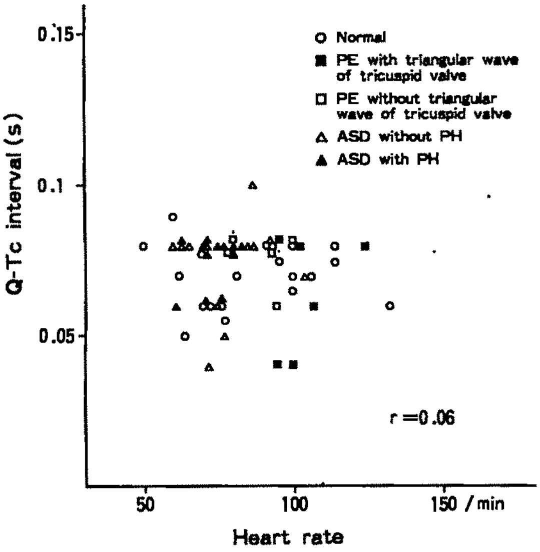

Fig. 4 *The Q-Tc interval plotted against heart rate for the four groups. Correlation coefficient shown are for the control group.*

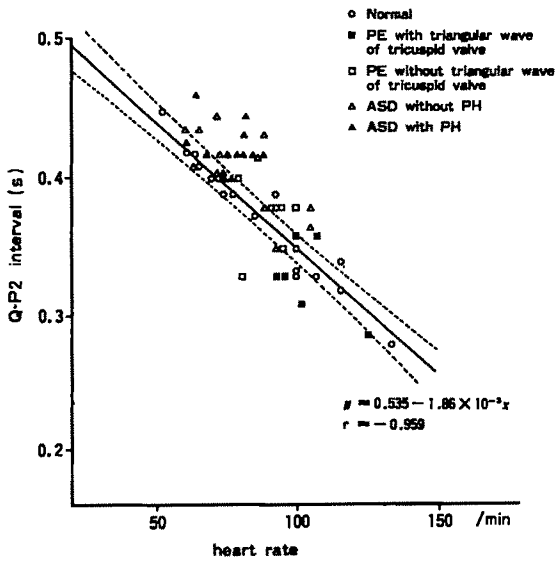

Fig. 5 *The Q-P2 interval plotted against heart rate for the four groups. Regression line and correlation coefficient shown are for the control group.*

Table 3 *Measurement of right and left-sided cardiac interval data*

Case No.	*Time after onset*	*Tricuspid valve*				*Mitral valve*			
		RR interval	*P2-Tc interval*	*To-Tc interval*	$\frac{To\text{-}Tc}{P2\text{-}Tc}$	*RR interval*	*A2-Mc interval*	*Mo-Mc interval*	$\frac{Mo\text{-}Mc}{A2\text{-}Mc}$
1	10 d	0·57	0·28	0·14	0·50	0·57	0·34	0·3	0·88
2	24 h	0·59	0·34	0·20	0·58	0·57	0·33	0·3	0·91
3	12 h	0·57	0·30	0·17	0·57	0·58	0·35	0·31	0·89
4	20 d	0·55	0·28	0·17	0·61	0·57	0·34	0·3	0·91
5	12 h	0·66	0·34	0·20	0·58	0·59	0·35	0·28	0·80
Mean ± SD		0·588 ± 0·038	0·308 ± 0·027	0·176 ± 0·022	0·568 ± 0·037	0·576 ± 0·008	0·342 ± 0·007	0·298* ± 0·01	0·878* ± 0·04

P2-Tc interval, the interval from closure of pulmonary valve to closure of tricuspid valve;
To-Tc interval, the interval from opening of tricuspid valve to closure of tricuspid valve;
A2-Mc interval, the interval from closure of aortic valve to closure of mitral valve;
Mo-Mc interval, the interval from opening of mitral valve to closure of mitral valve.
Asterisk(*) shows significant difference when compared with the corresponding values of right ventricle.

cases, whereas the paradoxical motion of the interventricular septum was not recognised.

In summary, we reported striking abnormalities of the tricuspid valve echocardiogram of pulmonary embolism, which are presumably in part related to the increased pulmonary artery pressure though there may well be other explanations. Further clinical and experimental studies are required to clarify the pathogenesis of the abnormalities of tricuspid valve motion in diastole and its significance in the evaluation of impaired right ventricular function in pulmonary embolism.

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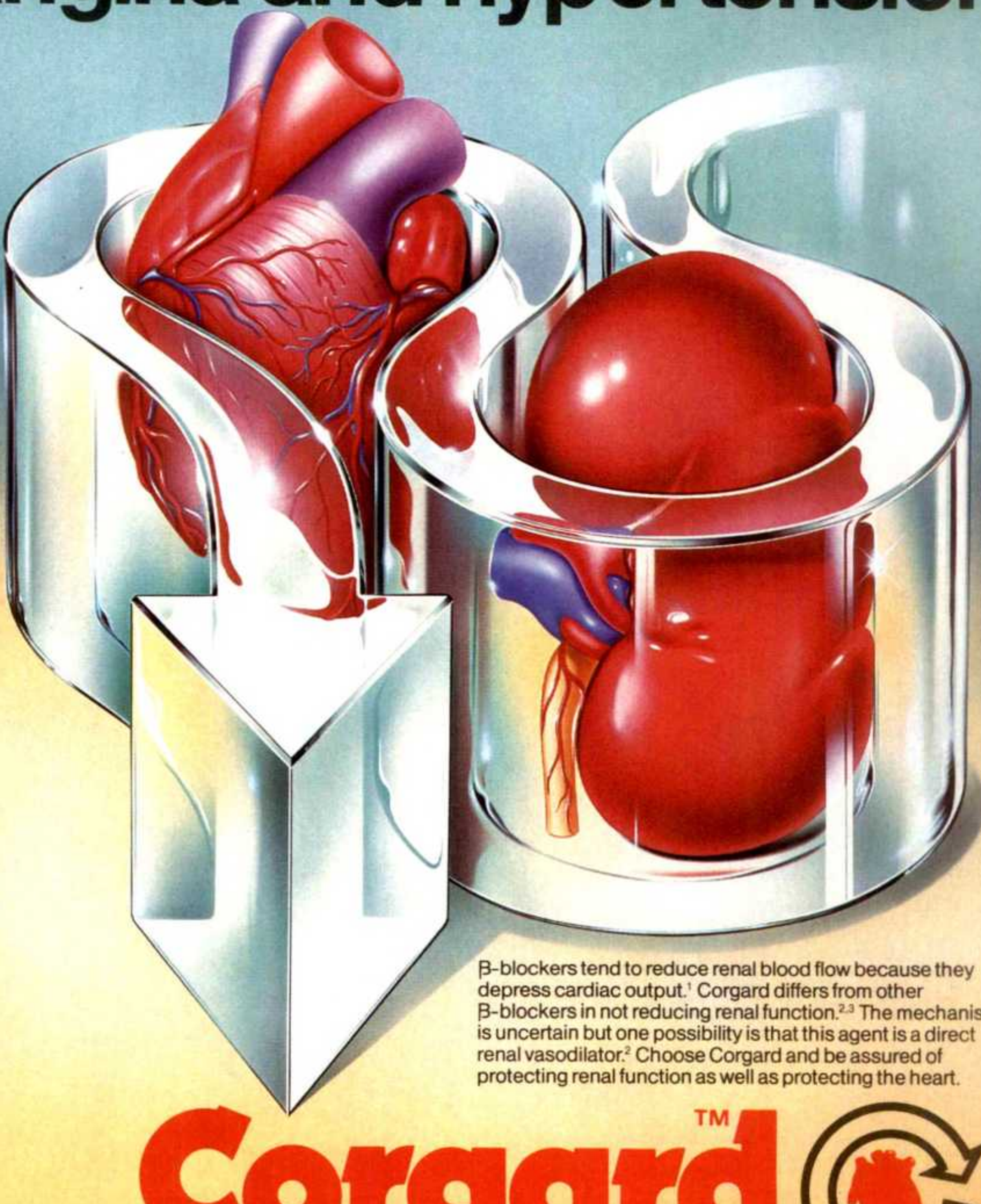

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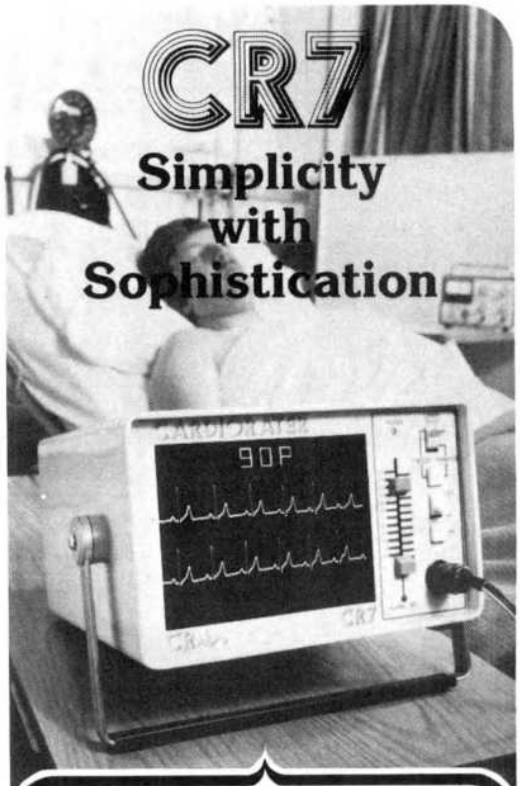

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Br Heart J 1982; 47: 461–7

Apex two dimensional echocardiography
Alternative approach to quantification of acute myocardial infarction

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SUMMARY Apex echocardiography has been chosen as an approach to detect and quantify acute myocardial infarction because the usual parasternal acoustic windows are often occluded. Fifty-three patients were studied, all within 12 hours after the onset of symptoms of their first myocardial infarction. Three apical long axis views were obtained, that is the two and four chamber views, and the right anterior oblique equivalent or three chamber view. Satisfactory echocardiograms were obtained in 48 patients (91%). The individual apical views were divided into equal segments and the area of asynergy was estimated in each view.

Left ventricular asynergy was present in all 48 patients. In 46 patients a positive correlation between the electrocardiogram and the echocardiogram was obtained, as far as infarct localisation was concerned. The estimated asynergic area correlated well with the peak value of the isoenzyme of creatine kinase (CK MB).

Apex echocardiography is a reliable alternative method of detecting and quantifying myocardial infarction soon after the onset of symptoms.

The immediate and long term prognosis of patients with an acute myocardial infarction depends largely on the site and extent of the infarcted myocardium.[1-3] It is of clinical significance, therefore, to be able to obtain reliable data regarding these features early after the onset of symptoms.

Various non-invasive techniques to determine infarct size have been developed recently,[4-6] of which echocardiography appears particularly useful since it can be performed at the bedside, involves no risk for the patient, is reproducible, and is capable of visualising the entire left ventricular wall.[7] In animal[8-10] and human[11-13] studies the regional wall motion abnormalities that occur with myocardial infarction have been visualised on two dimensional echocardiography and used to quantify the necrotic area. The success rate of obtaining adequate echocardiographic results in patients with an acute myocardial infarction, however, is limited[11 14] since the parasternal acoustic windows are often closed because of chronic lung disease.

It is for this reason that we used the site of the cardiac apex for the two dimensional echocardiographic localisation and quantification of regional wall motion abnormalities in patients with an acute myocardial infarction.

Accepted for publication 7 January 1982

Subjects and methods

Fifty-three consecutive patients (45 men; eight women) with a first myocardial infarction were studied. Their average age was 57 years (range 36 to 82). Acute myocardial infarction was documented by a typical clinical history, diagnostic Q waves on the electrocardiogram, and elevation of the isoenzyme of creatine kinase (CK MB).

Echocardiographic examination was performed in all patients within 12 hours after the onset of symptoms. Serial CK MB determinations were performed on admission and repeated every four hours thereafter until the peak value was reached.[15] A routine 12 lead electrocardiogram was obtained on admission and repeated every 12 hours during the first three days in hospital. The electrocardiographic infarct localisation was determined according to the criteria of the New York Heart Association.[16]

TWO DIMENSIONAL ECHOCARDIOGRAPHY

All echocardiographic studies were performed using a commercial mechanical sector scanner (Eko-Sector 1, Smith Kline Instruments) with an 82° sector arc and a 2·25 MHz transducer. The images obtained were stored on videotape for analysis by two observers.

All patients were studied in the left lateral decubitus position. The transducer was placed at the point of maximal impulse of the cardiac apex and the sector was directed towards the left atrium (Fig. 1). The apical four chamber view was first obtained showing the inlet part of the ventricular septum together with the apex and posterolateral wall of the left ventricle.[17-19] By rotating the transducer approximately 60 degrees clockwise a three chamber view was obtained comparable with the right anterior oblique equivalent. This view shows the outlet part of the ventricular septum, the apex, and the posterior wall of the left ventricle. A two chamber view was obtained by rotating the transducer approximately 60 degrees counterclockwise. This view shows the anterolateral and inferior wall of the left ventricle and the apex.[20]

ECHOCARDIOGRAPHIC ANALYSIS

Left ventricular wall motion of each study was analysed for the presence and extent of asynergy by two investigators who had no prior knowledge of the clinical status of the patient. The results were compared and occasional discrepancies were resolved by consensus. Precomparison interobserver variation for extent of asynergy was low ($r=0·95$). Asynergy was defined as hypokinesia, akinesia, or dyskinesia, as judged by the overall visual impression after reviewing each study in real time, slow motion, and stop frame formats.

Asynergy was termed "anterior" if it occurred in the apical, septal, or anterolateral regions and "inferior" if it occurred in the posterior, posterolateral, or inferior regions of the left ventricle. The basic principles used to estimate infarct size are shown schematically in Fig. 2. Each apical long axis view was divided into equal segments, and the estimated asynergic area was expressed as a percentage of the total number of segments.

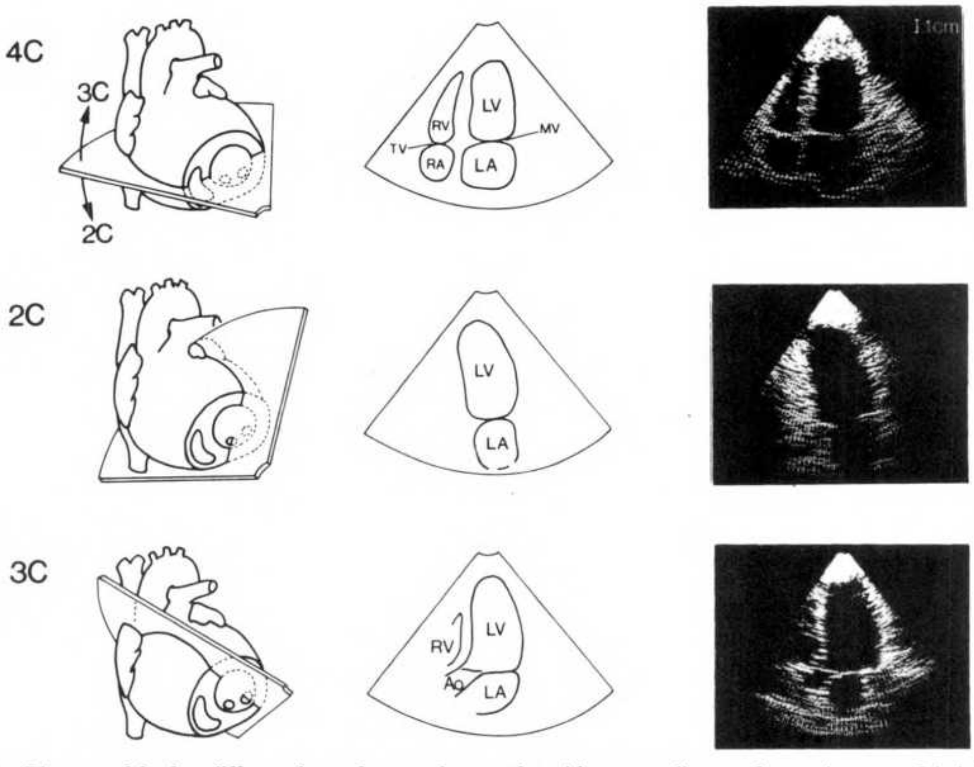

Fig. 1 *Diagrams of the three different planes of transsection, together with corresponding stop frames. Ao, aorta; LA, left atrium; LV, left ventricle; MV, mitral valve; RV, right ventricle; TV, tricuspid valve; 4C, four chamber view; 2C, two chamber view; 3C, three chamber view.*

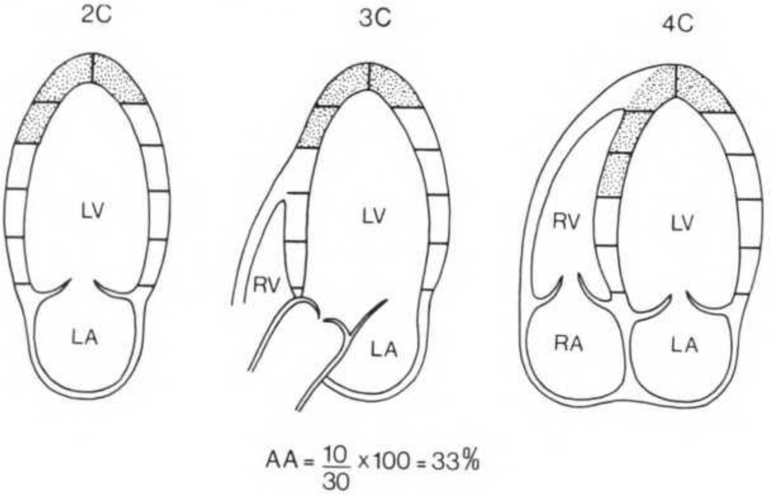

Fig. 2 *Schematic diagram showing the three apical long axis views. The left ventricular free wall and septum is divided into equal segments. The asynergic area (AA) of the left ventricular wall (dotted segments) is expressed as a percentage of the total number of segments (30). In this example a total infarct size of 33% is obtained. Abbreviations as in Fig. 1.*

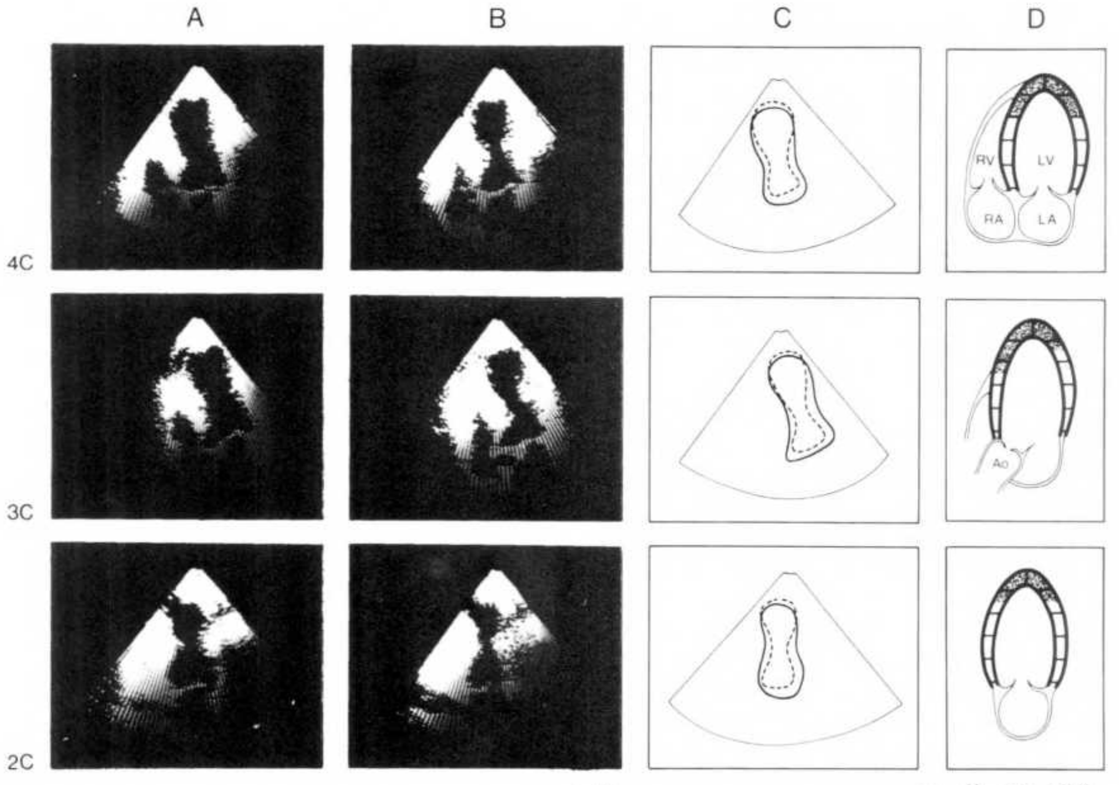

Fig. 3 *The panels A and B show the end-diastolic and end-systolic stop frames of each of the three long axis apical views in a patient with an acute anterior infarction, eight hours after onset of symptoms. Panel C shows the diastolic (solid line) and systolic (dotted line) outlines of the left ventricle. There is extensive asynergy. Note also the abnormal diastolic configuration of the left ventricle. In panel D the dotted segments represent the visually estimated asynergic area (AA) of the left ventricular wall, calculated at 37%. Abbreviations as in Fig. 1.*

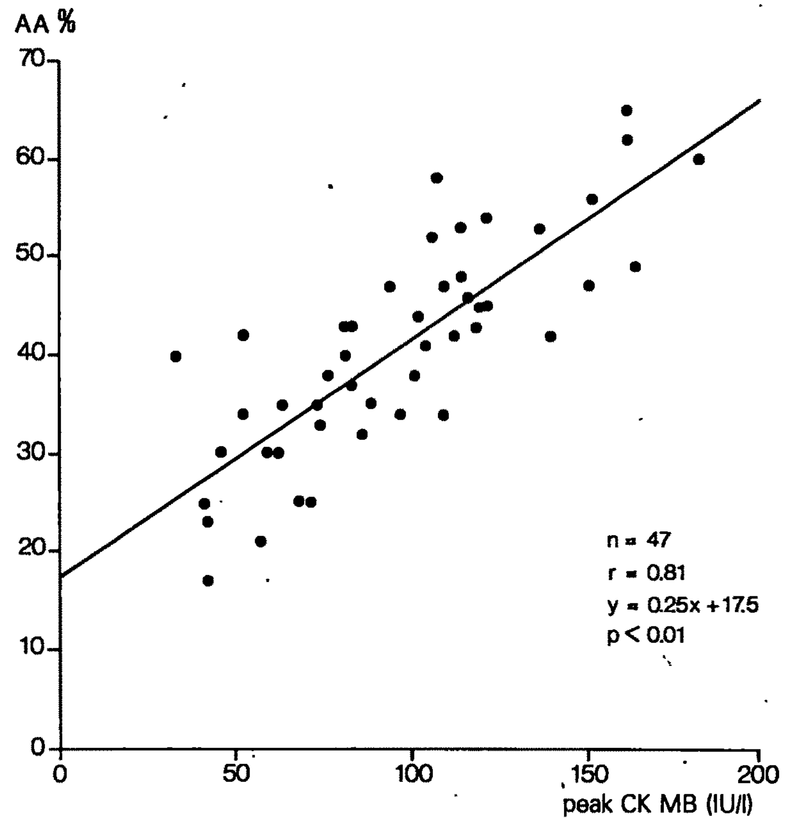

Fig. 4 *Diagram of the correlation between the peak value of CK MB and the echocardiographically estimated infarct size (AA). Abbreviation as in Fig. 2.*

Results

In 48 (91%) of the 53 patients (40 men; eight women) a complete and adequate two dimensional echocardiographic study was obtained (Fig. 3). Left ventricular asynergy was present in each of the 48 patients.

The unsatisfactory results in the five patients were caused by the left lung overlying the anterolateral left ventricular wall in the two chamber view.

LOCALISATION OF MYOCARDIAL INFARCT

The electrocardiographic site of infarction was anterior in 24 patients, inferior in 18, and anteroinferior in six patients. The echocardiographic site of infarction was the same in 46 of the 48 patients.

Discrepancy between the electrocardiogram and echocardiogram was present in two patients. One patient had an isolated inferior wall infarction on the electrocardiogram while the echocardiogram disclosed additional involvement of the ventricular septum. The other patient had an isolated anterior wall infarction on the electrocardiogram, but the echocardiogram showed asynergy of the apico-septal wall as well as asynergy of the posterior wall.

QUANTIFICATION OF INFARCT SIZE

Using the three cross-sections, infarct sizes could be quantified in each of the 48 patients. A correlation with the peak CK MB could be obtained in 47 patients, since one patient died within 18 hours after onset of symptoms. The correlation between both variables is shown in Fig. 4.

POST-MORTEM CORRELATION

During the period of this study only one patient died. This patient had extensive asynergy of the apical, septal, and anterolateral wall on the echocardiogram. The diastolic configuration, moreover, showed a distinct outward bulging of the affected area (Fig. 5A).

Necropsy showed an extensive transmural

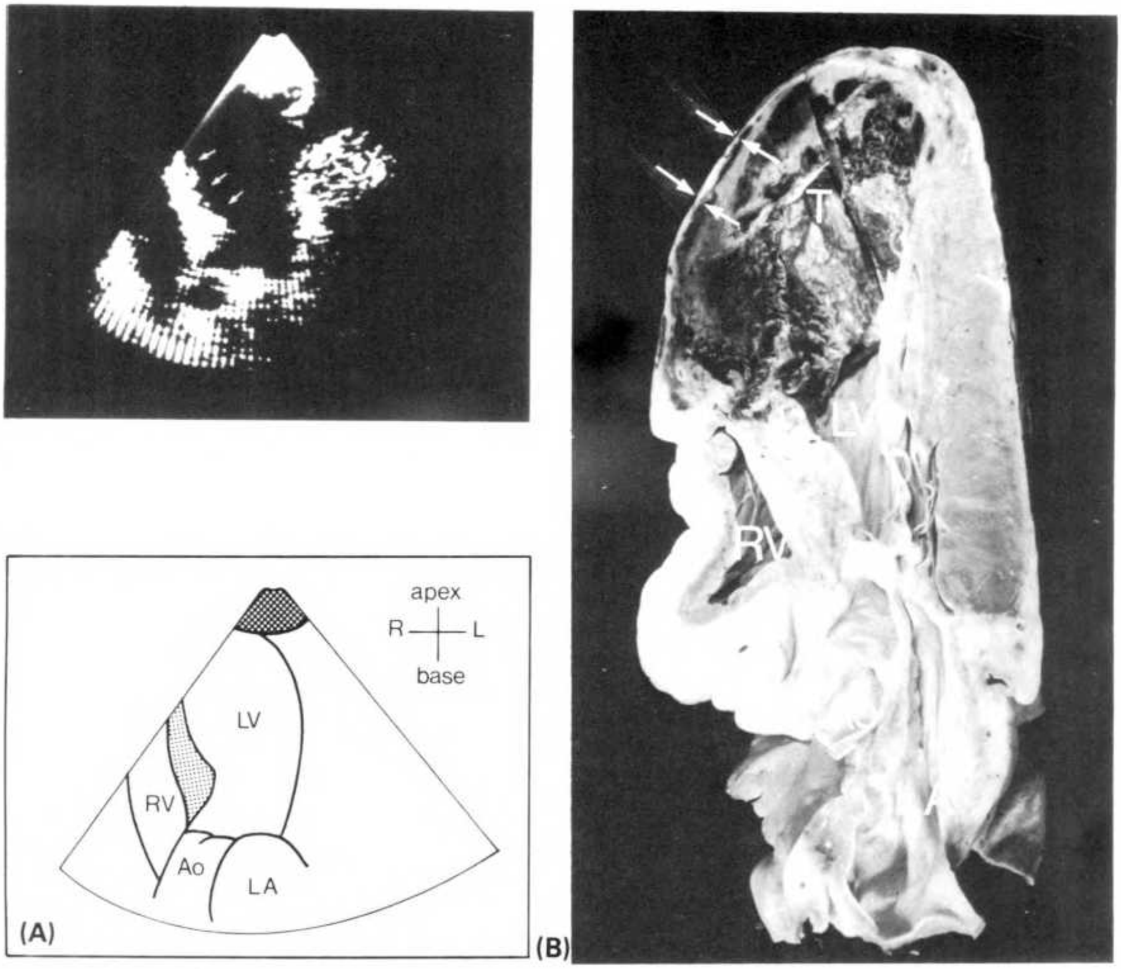

Fig. 5 *(A) End-diastolic three chamber view in a patient with an acute anterior infarction, who died 18 hours after admission. Note the obvious thinning of the septum (arrows) and distortion of the shape of the left ventricle. At the time of this study no intracavitary thrombus was identified. (B) A cross-section through the heart of the same patient comparable to the apical three chamber view. There is an extensive anteroseptal infarction with extreme wall thinning (arrows). Part of the left ventricular cavity is filled with thrombus (T).*

anteroseptal myocardial infarction of recent onset, which also extended onto the apex and the lateral free wall. An apical aneurysm was present (Fig. 5B). Rupture of the free wall had occurred leading to tamponade as the ultimate cause of death.

Quantification of the infarct size was performed using similar three cross-sections as used echocardiographically. Gross inspection thus disclosed a visually estimated infarct size of approximately 45%.

Discussion

Echocardiography is accepted as a reliable method of detecting wall motion abnormalities in patients with an acute myocardial infarction.[21-23] Unfortunately, the parasternal acoustic windows are often occluded in patients with coronary artery disease because of accompanying pulmonary disease. On the other hand, the site of the cardiac apex is often readily amenable to ultrasound penetration. In many patients with myocardial infarcts, particularly those with anterior wall infarction, the apex of the left ventricle is also involved[24 25] and, hence, because of apical dilatation, contributes to the size of this acoustic window. With this approach adequate echocardiographic images were obtained in 91% of the patients. This percentage is in accordance with that of reports in which apical long axis views were applied to determine left ventricular volumes,[20 26 27] but is better than the figures reported when only parasternal acoustic windows were used.[11 14]

CORRELATION BETWEEN SITE OF ASYNERGY AND ELECTROCARDIOGRAM

The abnormalities in wall motion were almost totally restricted to the region that correlated with the electrocardiographic infarct site. This finding can be explained by patient selection, since all of the patients were having their first myocardial infarction. A discrepancy was present in only two of the 48 patients. The electrocardiogram of one of these showed an isolated inferior infarction, whereas the echocardiogram disclosed additional asynergy of the adjacent septum. There is still uncertainty as to whether or not the septum was truly infarcted.

Clinical and experimental studies have shown that segments of the left ventricle adjacent to a region of infarction may exhibit asynergy and yet be normal morphologically.[28–30] On the other hand, inferior infarction may well extend into the interventricular septum without producing characteristic electrocardiographic changes.[25 31]

The echocardiogram of the second patient disclosed asynergy of the apex and septum, in keeping with the electrocardiogram, but in addition showed asynergy of a non-adjacent segment of the posterior wall. The posterior area of the left ventricle is difficult to evaluate electrocardiographically[32] and this may explain the discrepancy.

QUANTIFICATION OF INFARCT AREA

As previously outlined, we have taken asynergy as an indicator for myocardial infarction, though we realise that this is not necessarily always the case. At present, however, in judging infarct size this particular feature is the most reliable echocardiographic variable. We showed a linear correlation between infarct size judged from the echocardiograms and that based on the peak values of CK MB, indicating the reliability of the method employed. This conclusion is in keeping with the observation that wall motion abnormality correlates with enzymatic estimates of infarct size.[33]

It is important, furthermore, that the three cross-sections do not cover all of the ventricular wall. Despite this restriction, asynergy was encountered in all patients. This could be explained by the fact that the lowest value of the peak CK MB in our population was 33 IU/l (normal: 4 IU/l or less), so that the infarcts were probably all sufficiently large to be encountered in at least one of the echocardiographic sections. The asynergic area in 47 patients ranged from 17 to 66%. Some of these values are likely to be exaggerated since a true loss of myocardium of more than 40% is usually fatal.[1] Moreover, it is well known from experimental and clinical studies that abnormalities in wall motion extend beyond the region of actual infarction.[13 34] It is of interest, in this regard, that the only patient in this study who died had an estimated infarct size on echocardiographic grounds of approximately 55%, while the necropsy disclosed an infarct of approximately 45%.

From a practical point of view it thus appears that the usual percentages of myocardial loss quoted to predict prognosis, which are all related to the total left ventricular myocardial mass, need an adjustment when based on this particular echocardiographic approach. In our hands this alternative method provides a reliable option in the quantification of infarct size.

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Scimitar syndrome in infancy
Role of embolisation of systemic arterial supply to right lung

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SUMMARY Four infants with scimitar syndrome are described. All had a systemic arterial supply to part of the right lung and one was treated successfully by embolisation of this vessel. The role of the systemic arterial supply to the right lung in producing symptoms in infants with scimitar syndrome is discussed.

The scimitar syndrome[1] is a well recognised radiological entity in which anomalous drainage of one or more of the right pulmonary veins to the inferior vena cava produces a characteristic shadow at the right cardiac border. The syndrome is variable in its expression and though the majority of reported cases have been older children or adults[2,3] with only minimal symptoms, occasional cases have been described in whom intractable symptoms developed early in infancy. Some degree of hypoplasia of the right lung with rotation of the heart into the right hemithorax is common and in many cases the right lung receives an aberrant arterial supply from a systemic artery. Additional intracardiac malformations are well recognised but relatively uncommon.

We have recently seen four infants who developed severe symptoms within the first weeks of life. All had an arterial supply to the right lung from a systemic artery and one was treated successfully by selective embolisation of this artery.

Case reports

CASE 1

This patient presented at 3 days of age with dyspnoea. The cardiac impulse was predominantly to the right of the sternum and a soft systolic murmur was audible. The chest *x*-ray film showed dextrocardia and cardiac enlargement, and the electrocardiogram showed an rS pattern across the precordium. Cardiac catheterisation was performed at 8 days of age because of increasing cardiac failure and the haemodynamic findings are summarised in the Table. Bronchoscopy and bronchography at 6 months of age showed only two major bronchi in the right lung, supplying the upper and middle lobes. The trachea and left bronchus were normal. In spite of vigorous treatment of congestive cardiac failure and respiratory infections the condition of the infant deteriorated and a second cardiac catheterisation was perfomed at 7 months. Angiography showed the heart to be displaced to the right with enlargement of the right atrium. The right pulmonary artery gave branches only to the upper and middle lobes while the lower lobe was supplied from a large vessel arising from the coeliac axis. Below the origin of this artery the aorta abruptly narrowed in calibre (Fig. 1) but no pressure gradient was recorded. An atrial septal defect was present and all the right pulmonary veins drained to the inferior vena cava. Open heart surgery was performed to close the atrial septal defect (sinus venosus type) but immediately after operation it was apparent that there was a considerable shunt through the sequestered right lower lobe. A pneumonectomy was performed 24 hours later but the patient died within hours. Necropsy confirmed the known anatomical findings.

Table *Cardiac catheterisation data in four patients*

Case No.	*Age at catheter (days)*	*Pressure (mmHg)*		*Qp/Qs*
		MPA	*Systemic*	
1	8	50	64	3·5
1	194	65	70	2·0
2	13	85	90	2·2
3	45	40	105	3·0
3	56	55	100	—
4	4	80	80	2·0
4	23	75	78	3·0

CASE 2

This patient was first seen at 9 days of age with dyspnoea and a systolic murmur. The chest *x*-ray film showed mesocardia, cardiac enlargement, and pulmonary plethora. The electrocardiogram showed an rS pattern across the left precordium. Cardiac

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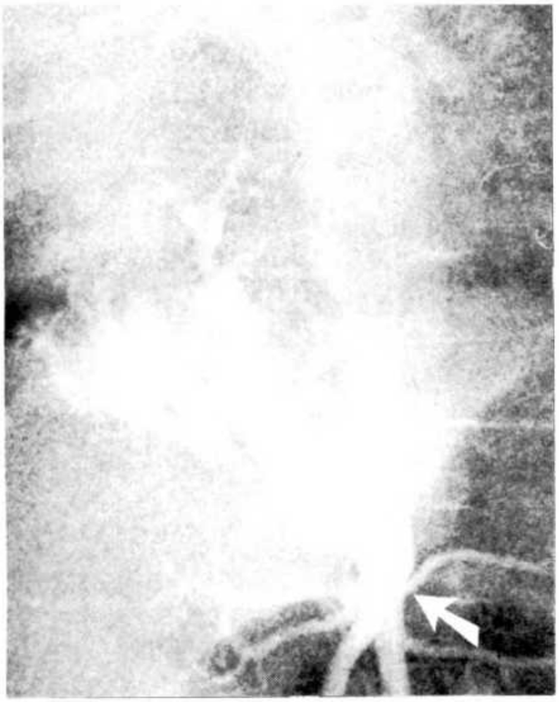

Fig. 1 *Aortogram in case 1. A large artery arises from the coeliac axis to supply the right lower lobe. At the point of origin of this artery (arrow) the aorta narrows abruptly.*

catheterisation at 13 days confirmed the presence of the scimitar syndrome with drainage of all the right pulmonary veins to the inferior vena cava. The branching pattern of the right pulmonary artery was abnormal with only two main divisions, but the lower zone of the lung received an additional arterial supply from a large vessel which arose from the coeliac axis. At this point there was an abrupt change in calibre of the descending aorta. Because of increasing cardiac failure an attempt was made, at 16 days, to eliminate flow through this aberrant vessel by embolisation using a catheter introduced through the femoral artery. Unfortunately the aberrant artery could not be entered and the procedure was abandoned. Two months later, after a period of cardiac failure and respiratory infections requiring assisted ventilation, a right pneumonectomy was performed, but the infant died in the immediate postoperative period. Necropsy confirmed the known findings and histological examination of the lungs showed intense muscularisation of pulmonary arteries and arterioles, not only in the right lower zone but also in the left lung. The right lung was moderately hypoplastic and had no visible fissures.

CASE 3

This patient had Hirschsprung's disease. An ileostomy was performed in the first week of life and the patient was admitted to the cardiac unit at 6 weeks of age with

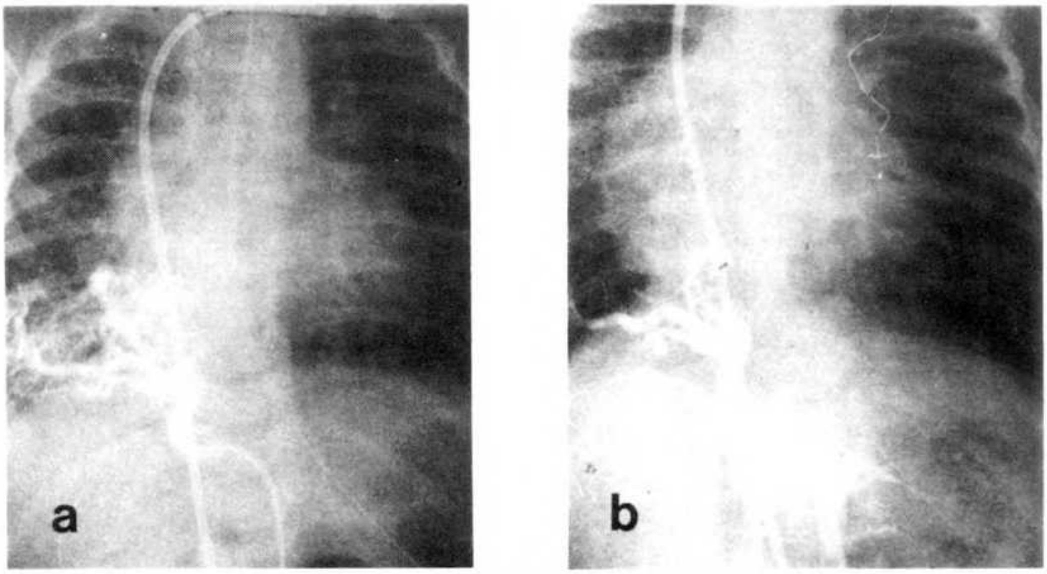

Fig. 2 *Selective angiogram in the aberrant artery in case 3 (a) before and (b) after embolisation. After embolisation though the proximal part of the artery is patent there is no capillary phase and no filling of the inferior vena cava or right atrium.*

dyspnoea. A soft systolic murmur was present and the chest *x*-ray film showed laevocardia, with cardiomegaly and pulmonary plethora. The electrocardiogram showed evidence of right atrial and right ventricular hypertrophy. Cardiac catheterisation was performed soon after admission. Angiography showed the heart to be displaced slightly to the right with considerable dilatation of the right atrium. The right pulmonary artery had a normal branching pattern and the right pulmonary veins drained into the inferior vena cava. The left upper lobe pulmonary vein entered the innominate vein. A large vessel from the coeliac axis penetrated the diaphragm to give a second arterial supply to the right lower lobe. The aorta tapered abruptly below the origin of this artery. During the following two weeks, increasing cardiac failure and respiratory difficulties developed. At 56 days, when the infant weighed 2·9 kg a 4FG catheter with end and side holes was introduced from the femoral artery and manipulated into the aberrant artery. The catheter position was verified by selective angiography and 2 to 3 mm Gelfoam fragments were injected through the catheter until the artery was obstructed (Fig. 2) After this procedure there was a rapid improvement in the infant's condition (Fig. 3) and she was discharged from hospital three weeks later. Progress was satisfactory at 7 months of age.

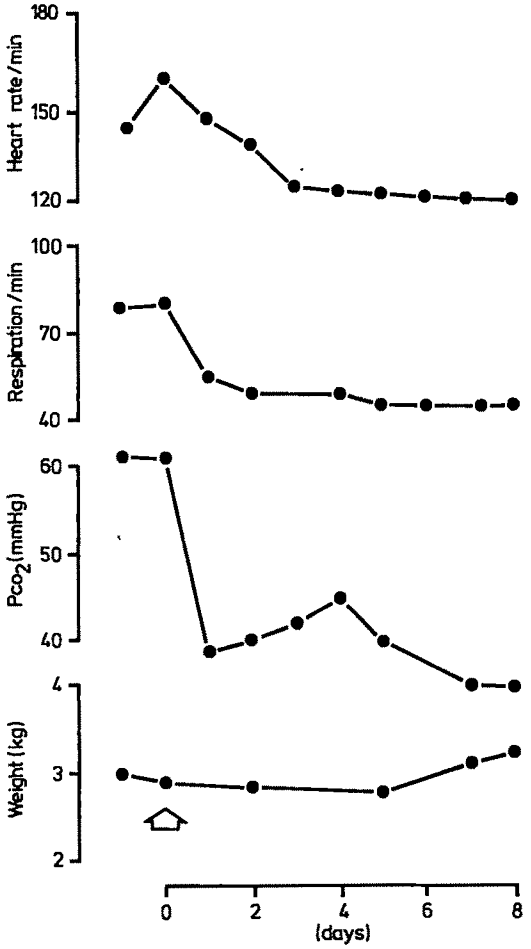

Fig. 3 *Heart rate, respiratory rate,* P_{CO_2}, *and weight of case 3 before and after embolisation of aberrant artery. The arrow indicates the date of embolisation.*

CASE 4

This infant presented on the first day of life with cyanosis and was found to have dextrocardia on the chest *x*-ray film. Close inspection of the film disclosed an opacity behind the heart compatible with a scimitar shadow, and cardiac catheterisation at 4 days of age confirmed this diagnosis. Though the right lung was very hypoplastic, the branching of the right pulmonary artery was normal. All the right pulmonary veins entered the inferior vena cava. An aberrant vessel from the region of the renal arteries gave a second arterial supply to the right lower lobe. The baby subsequently developed severe cardiac failure with disturbance of serum electrolyte concentrations secondary to diuretic therapy. Embolisation of the aberrant artery was performed at 23 days using a 3FG catheter introduced percutaneously from the femoral artery and Gelfoam fragments soaked in 50% dextrose. The baby was critically ill at the beginning of the procedure and though the artery was successfully occluded she remained in low cardiac output, developed renal failure, and died four days later. The renal arteries were shown to be patent on an aortogram after embolisation. Consent for necropsy was refused.

Discussion

The majority of reported cases of the scimitar syndrome have been older children or adults in whom symptoms have been minimal or absent.[2 3] The good prognosis for most of these patients is in pronounced contrast to the outlook for those patients who develop symptoms early in infancy. The initial descriptions by Chassinat[4] and Cooper[5] in 1836, were followed by a number of accounts which described individual infants who died within the first year, though in many cases the nature of the cardiac defect was not recognised during life.[6–11] The patient of Chassinat[4] probably died as a result of coexisting pulmonary atresia, but the remaining patients did not have major cardiac defects which might have accounted for their death. Neill *et al.*[1] reported the case of an infant who developed symptoms at 7 months of age but who survived until a pneumonectomy was performed at 2½ years.

A number of factors may influence the development of symptoms in the scimitar syndrome. The normal right lung carries approximately 55% of the pulmonary blood flow.[12] In the absence of any additional site of shunting, anomalous drainage of all the right pulmonary veins to the systemic veins might therefore be expected to result in a left to right shunt with a pulmonary to systemic flow ratio of about 2:1. A shunt of this size would be unlikely to produce symptoms in infancy and would probably be well tolerated even in the longer term. Extreme hypoplasia of the right lung may limit the size of the shunt to such an extent that no detectable rise in oxygen saturation may be recorded in the great veins or right heart, as in the cases reported by Kiely *et al.*[2] Conversely, an arterial supply to the right lung from the descending aorta may function as a large arteriovenous fistula and our experience suggests that it is the size of the shunt through these vessels which determines the presence and severity of symptoms in infancy. The abrupt change in calibre of the descending aorta distal to the origin of the aberrant vessel previously noted by Mortensson and Lundstrom[10] is perhaps an indication of the significance of the shunt in these subjects. Kiely *et al.*,[2] in a review of 67 reported cases, commented on the variability in size of these vessels and in many older asymptomatic patients they may be absent.

To our knowledge, successful treatment of a severely symptomatic infant with scimitar syndrome has not previously been reported. The infant described by Woody *et al.*,[13] however, deserves mention because of the similarities to the present cases. This patient[13] had hypoplasia of the right lung, a systemic arterial supply to the right lower lobe from the descending aorta, and coarctation of the aorta, but the right pulmonary veins drained via an azygos vein to the superior vena cava. At 1 month of age the aberrant arteries were ligated through a right thoracotomy and the azygos vein was anastomosed to the left atrium, with a dramatic fall in pulmonary artery pressure. Pneumonectomy became necessary within 24 hours of operation because of thrombosis of the azygos vein. Mortensson and Lundstrom[10] reported the case of a baby with the scimitar syndrome who developed symptoms at 9 days of age and subsequently underwent a pneumonectomy but who died at 1 year. In this patient the right pulmonary artery was absent. In many patients with the scimitar syndrome, including three of our own patients, parts of the right lung have a dual arterial supply from both the pulmonary artery and the descending aorta. It therefore seems appropriate to consider therapeutic measures which would conserve functioning lung where possible. Open heart surgery to divert the anomalous venous channel into the left atrium has been accomplished in older patients[14 15] but is unlikely to be successful in infants unless the shunt through the aberrant artery is also abolished. This may present considerable difficulty if pneumonectomy is to be avoided since the vessels tend to divide into many branches above the diaphragm.

Therapeutic obliteration of selected arteries by embolisation through a catheter has been used recently in a variety of situations.[16 17] Using this technique we were able to block the aberrant arterial supply to the right lung in two of the three patients in whom it was attempted, with a dramatic improvement in the condition of one patient. In the patient who died after embolisation the outcome was probably related to the poor condition of the patient at the start of the procedure, and a favourable result might have been achieved if intervention had been earlier. The rapid deterioration of this patient and the early changes of pulmonary vascular disease in both lungs of case 2 emphasise the need for urgent treatment in these cases. A similar pattern of pulmonary vascular change to our patient was seen in the patient reported by Neill *et al.*[1]

As yet there is insufficient information on which to base an accurate assessment of the risk of embolisation procedures in small babies, but evidence from large series of older patients suggests that the risk is acceptable.[16 17] In infants with the scimitar syndrome and an aberrant arterial supply to the right lung, the alternatives appear to be a thoracotomy to ligate the leash of vessels passing through the diaphragm, or an abdominal approach to ligate the vessel close to its origin. Both procedures may present considerable difficulties with the chance of only partial success. On the basis of our recent experience we believe that embolisation of the aberrant arterial supply may prove to be an effective palliative measure, permitting postponement of open heart surgery to connect the anomalous pulmonary veins to the left atrium until later in childhood.

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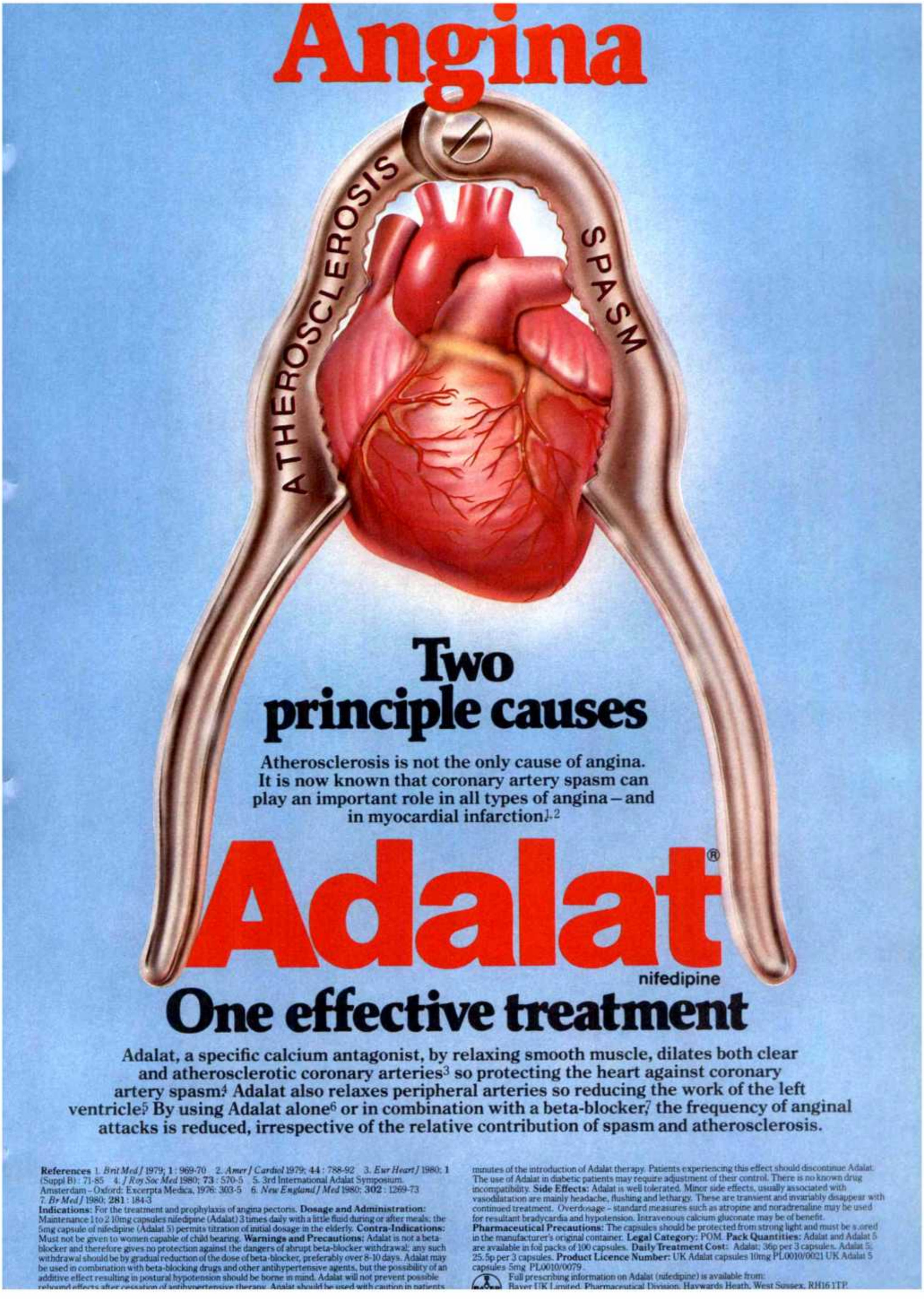

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References 1. *Brit Med J* 1979; **1** : 969-70 2. *Amer J Cardiol* 1979; **44** : 788-92 3. *Eur Heart J* 1980; **1** (Suppl B) : 71-85 4. *J Roy Soc Med* 1980; **73** : 570-5 5. 3rd International Adalat Symposium. Amsterdam – Oxford: Excerpta Medica, 1976: 303-5 6. *New England J Med* 1980; **302** : 1269-73 7. *Br Med J* 1980; **281** : 184-3

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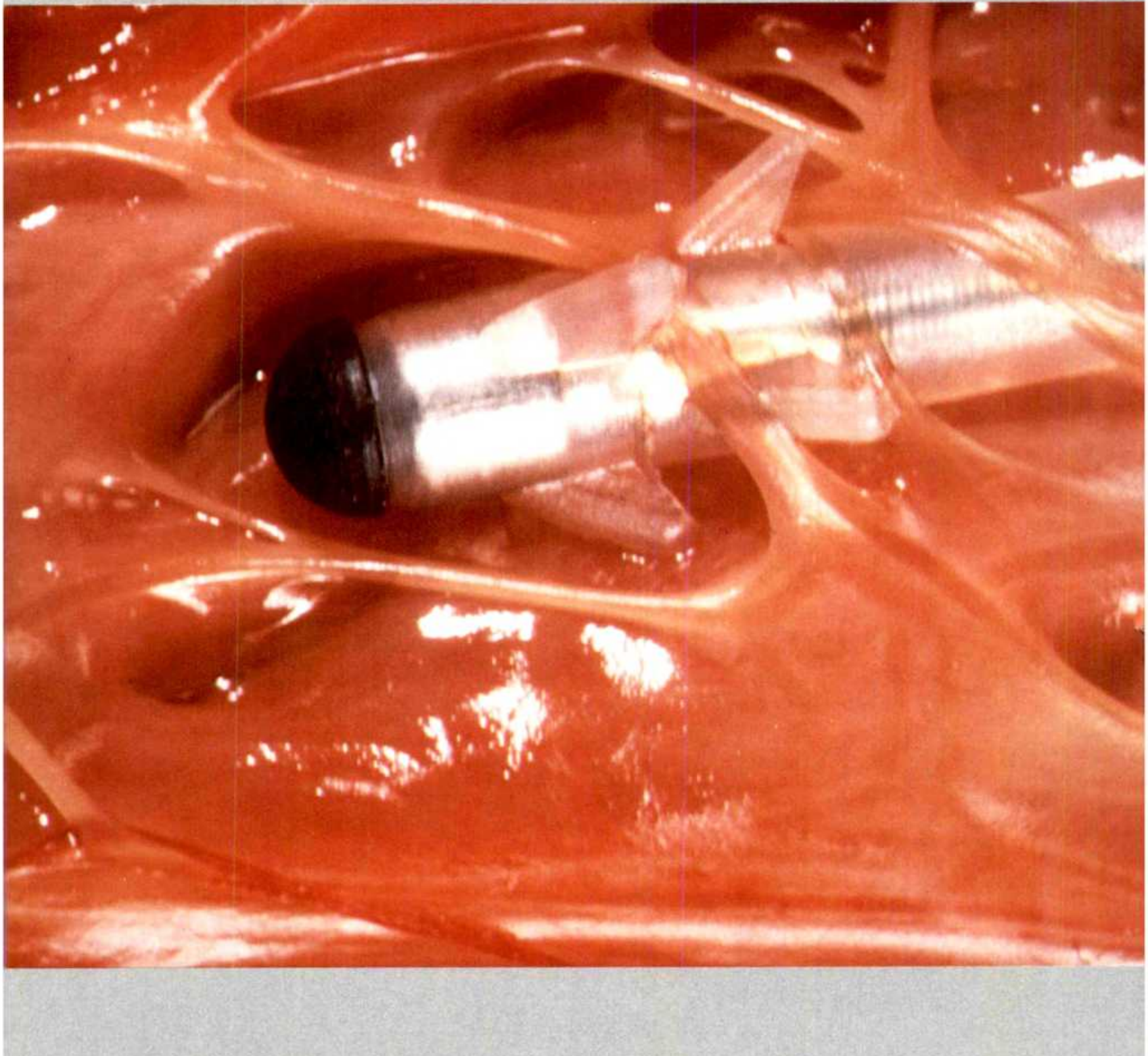

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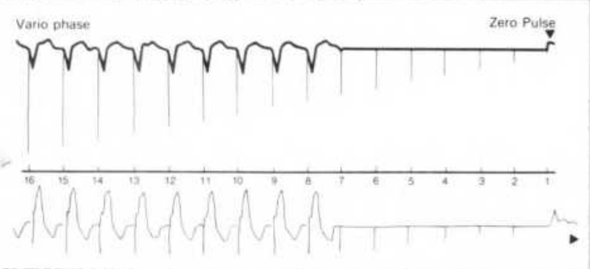

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Br Heart J 1982; 47: 473–82

Homograft replacement of aortic root with reimplantation of coronary arteries

Results after one to five years

JANE SOMERVILLE, DONALD ROSS

From Paediatric and Adolescent Unit, National Heart Hospital, London

SUMMARY Between 1976 and 1980, 26 patients aged 7 to 36 years had complete replacement of the aortic root with a valved homograft into which the coronary arteries were reimplanted. The main indication was the tunnel type of obstruction combining a hypoplastic valve ring, often with supra and subvalvar stenosis. Nineteen had previous operations for congenital left ventricular outflow obstructions.

There was one perioperative death and one late death from progressive pulmonary vascular disease. Relief of left ventricular outflow tract obstruction was achieved in a majority of cases and the valves were entirely competent. With increasing experience, the initial problems of malalignment and torsion of the coronary arteries and complete heart block have been largely overcome.

This operation provides an alternative technique for the management of diffuse left ventricular outflow tract obstruction and related problems in young patients. The long-term results of aortic homografts are well documented, and by eliminating the problems of aortic regurgitation it is anticipated that this may represent an advance in treatment.

The relief of "tunnel"[1] left ventricular outflow tract obstruction occurring as a primary lesion or after previous aortic valvotomy and resection of fixed subaortic stenosis is difficult and is associated with significant morbidity and mortality.[2] The problems are to fit an adequate aortic valve replacement into a small, hypoplastic aortic root, and to relieve the associated diffuse muscular subvalvar and sometimes supravalvar narrowing.

With the increasing numbers of reoperations on patients who have had previous surgery for various forms of aortic stenosis[3 4] a solution is urgently needed for this problem.

After adequate excision of the distorted, narrow aortic root and aortic valve, the left ventricular outflow tract opens up, and it becomes possible to put in an adult homograft aortic root and valve and reimplant the coronary arteries into the homograft.[5] This provides good relief of obstruction and was first performed in 1972 (DR) for the emergency replacement of an infected Starr valve; the patient has maintained a good clinical and haemodynamic result to date.

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It is now our practice to use this operation in young patients with complex left ventricular outflow obstruction. Since 1976, in the National Heart Hospital, the operation has been used in tunnel obstructions and other forms of aortic root and valve disease where simpler forms of aortic valve replacement or enlargement of the ring have not produced good results, and we report our experience of this technique from 1976 to 1980.

Technique

In managing the complex hypoplastic aortic root, the aim is to excise the whole tunnel area of thickened hypoplastic tissue, which often includes a supravalvar stenosis, the thickened valve, a hypoplastic ring, and additional subvalvar endocardial proliferation (Fig. 1a).

The upper limit of the incision is at least 1 cm above the point of commissural attachment of the valve, and the lower extent of the incision is across the outflow tract of the left ventricle at the point of insertion of the right coronary sinus into the septum anteriorly and across the subvalvar curtain of the mitral valve posteriorly. In the angle between the right and non-coronary cusps the incision skirts the

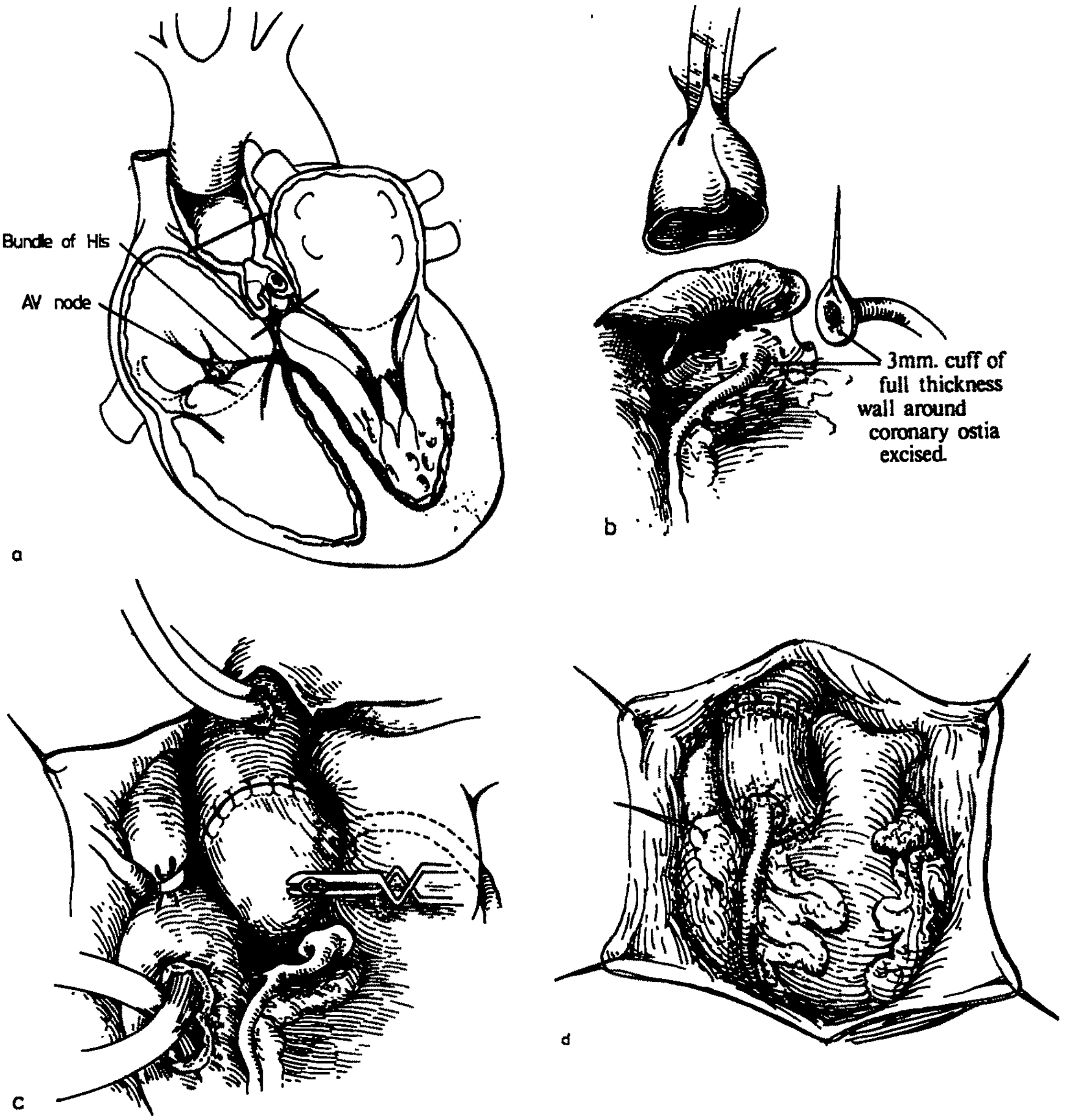
Bundle of His
AV node
a
b
3mm. cuff of full thickness wall around coronary ostia excised.
c
d

Fig. 1 *Drawings of stages of aortic root replacement with an aortic homograft and with reimplantation of the coronary arteries.. (a) Extent of excision of the aortic root and position of the conducting tissue. (b) The left coronary has been excised with a cuff of tissue and will be sutured into the new aortic root in the original position of the left coronary artery. (c) After completion of the upper suture line the aortic root is distended to determine the most appropriate site for attachment of the right coronary artery. (d) The completed aortic root and valve replacement as seen from the front.*

upper margin of the membranous septum in order to avoid the conducting tissue. The coronary orifices are preserved with a 2 to 3 mm cuff of surrounding aortic wall. Such an incision results in a remarkable enlargement of the left ventricular outflow and makes it possible to insert an adult sized aortic root of at least 2 cm in diameter.

Conventional hypothermic bypass is established and cardioplegic arrest of the heart is achieved with Ringer's solution and potassium (20 mg/l).

As a first step, the aorta is opened transversely (Fig. 1b) and once a decision to replace the root has been made it is completely transected and the upper end is freed from the pulmonary artery.

The coronary arteries are identified, and it is advisable to pass curved blunt probes into them to identify their direction at this stage and during their subsequent mobilisation. The aortic wall is incised in such a way as to allow a full thickness cuff of aortic wall about 3 mm around both coronary arteries (Fig. 1b), after which the remaining aortic wall is excised boldly across the anterior mitral valve cusp and more circumspectly anteriorly across the membranous septum so as to clear the conducting tissue. The excision from the septum anteriorly leaves some fibrous remnants for the later attachment of sutures to the muscle. Any excess subvalvar endocardial proliferations and extensions can now be enucleated by blunt dissection and if the subvalvar hypertrophy is gross a formal subvalvar myotomy and wedge resection of muscle can be added.

With a bougie in place in the left coronary artery this vessel should be mobilised freely and carefully so as to avoid subsequent tension or torsion when it is reattached to a larger aortic homograft.

Multiple interrupted 4/0 Prolene sutures are now used to attach the lower margin of the horizontally trimmed homograft to the corresponding areas of the previous valve excision. At least 24 sutures are required, dividing the circumference into four sections with six to eight sutures in each. It is convenient to tie these down over a thin 4 mm strip of Teflon felt to aid haemostasis and to avoid cutting through the muscle of the homograft.

The left coronary artery is now attached to a corresponding excised orifice in the left coronary sinus of

Table 1 *Dominant lesion for which previous surgery and/or root replacement was performed*

Case No.	*Previous operation*	*Age (y)*	*Aortic valve and root replacement*					
			Dominant lesion	*Tunnel obstr.*	*Age (y)*	*Myotomy*	*Wedge resection*	*Other surgery at same time*
1			AVS	+	11	—	—	—
2			AVS	+	7	+	+	Ligation of PDA, repair of LCA
3			AVS	+	12	+	+	—
4	Aortic valvotomy + relief supraAS	11	SupraAS	+	17	+	+	Repair of RCA
5	Aortic valvotomy	11	AR	—	16	—	—	—
6			AR	—	15	—	—	—
7	AVR-Starr for AS+AR	26	AR	—	36	—	—	—
8	Aortic valvotomy AVR-Hancock for AS	6 15	AVS	+	16	+	+	CVG's to LAD and marginal branch of circumflex
9	Resection of fixed subAS	9	SubAS	+	20	+	+	—
10	Aortic valvotomy	8	AVS	—	22	—	—	—
11			AVS	+	14	—	—	—
12	Aortic valvotomy Aortic valvotomy	3 8	AVS	+	13	+	+	—
13			AR (congen.)	—	14	—	—	Mitral annuloplasty
14	Resection coarct.; AVR-homograft for AS	11 14	AR	—	25	—	—	CVG to RCA; insertion of pacemaker for CHB
15	Aortic valvotomy	6	AVS	+	13	+	+	—
16	Resection of fixed subAS	10	SubAS	+	14	+	+	—
17	Resection of fixed subAS	10	SubAS	—	15	+	—	—
18	Resection coarct.; aortic valvotomy	1/12 5	AVS	+	8	+	+	—
19	Closure of VSD+AVR-homograft for AR	5	AR	—	8	—	—	—
20	Aortic valvotomy	15	AR	—	21	—	—	—
21	Resection of fixed subAS	15	SubAS	+	27	+	—	—
22	AVR-homograft for AR (SBE); AVR-Starr for AR (SBE)	19 23	AR	—	32	—	—	—
23	Repair of 1° ASD+ repair of cleft mitral and tricuspid valves; AVR-C/E xenograft for AS+repair VSD; repair of periprosthetic leak+ closure VSD	2 13 14	SubAS/AR	—	14	—	—	Closure of VSD+repair of cleft mitral valve
24			AVS	—	27	—	—	—
25	Aortic valvotomy; AVR-homograft for AS+AR	6 14	AVS	—	18	—	—	—
26	Relief of supraAS	4	AR	+	12	—	—	CVG to LAD

AR, aortic regurgitation; AS, aortic stenosis; AVS, aortic valve stenosis; AVR, aortic valve replacement; C/E, Carpentier Edwards; CHB, complete heart block; Coarct., coarctation of aorta; Congen., congenital; CVG, coronary vein graft; LAD, left anterior descending; LCA, left coronary artery; Obstr., obstruction; PDA, persistent ductus arteriosus; RCA, right coronary artery; SBE, bacterial endocarditis; SubAS, subaortic stenosis; SupraAS, supra-aortic stenosis; VSD, ventricular septal defect; 1° ASD, ostium primum atrial septal defect.

the homograft and this is achieved with a closely placed continuous suture of 6/0 Prolene.

The upper margin of the homograft is then trimmed and sewn to the transected aorta with a continuous 4/0 Prolene suture.

With a temporary clamp on the right coronary ostium of the homograft the aortic clamp is released after exclusion of air and the new aortic root is observed under pressure (Fig. 1c). This enables haemostasis to be checked and, more important, the best point of attachment of the right coronary to be determined. This is a necessary precaution since the position of the right coronary is variable and may not correspond with the corresponding orifice on the homograft. An appropriate site for the right coronary is chosen; the aortic clamp is reapplied and the right coronary is attached in the same way as the left with a running 6/0 Prolene suture. The complete aortic valve and root replacement is shown (Fig. 1d).

Subjects

Between May 1976 and August 1980, 26 patients aged 7 to 36 years had total aortic valve and root excision and replacement with a "fresh" aortic homograft together with reimplantation of the coronary arteries.

After operation patients were examined at six monthly or annual intervals with repeated electrocardiograms, phonocardiograms, M-mode echocardiograms, and chest radiographs. Since 1978 two dimensional echocardiography has provided accurate additional information on the state of the aortic root, valve, and subvalvar region.

Recatheterisation was performed in 16 patients three weeks to 21 months after operation when agreed to by the patient and referring physician. Two patients (cases 8 and 16) had a second postoperative catheter study. Gradients across the left ventricular outflow tract were measured at rest and after isoprenaline challenge. At the same investigation, routine biplane ascending aortography to identify the reimplanted coronary arteries and to assess aortic regurgitation and cusp movement, and left ventricular angiography were done.

The dominant lesion for which previous surgery and/or aortic root replacement was performed has been summarised (Table 1).

Twelve patients had one previous operation and seven had two or three previous operations. Only seven had the procedure as a primary operation.

Preoperative state of patients

CLINICAL

The age distribution of the patients at the time of operation and the number of patients operated upon each year are shown (Fig. 2a and 2b). The youngest was 7 years and the oldest was 36 years (mean age 17 years 9 months); 16 were in the second decade. There were 15 male and 11 female patients. Eighteen had symptoms and eight were symptom free.

The indications for operation in the eight patients without symptoms were resting left ventricular outflow tract gradients ranging from 50 to 130 mmHg in five cases or severe aortic regurgitation in three; all had ST-T wave changes in left ventricular leads. The patient with a resting gradient of 50 mmHg had had a fixed subaortic stenosis removed seven years earlier and had developed a deteriorating electrocardiogram; isoprenaline produced a gradient of 100 mmHg. Left ventricular hypertrophy was present in 25 of the 26 patients and one had had left bundle-branch block

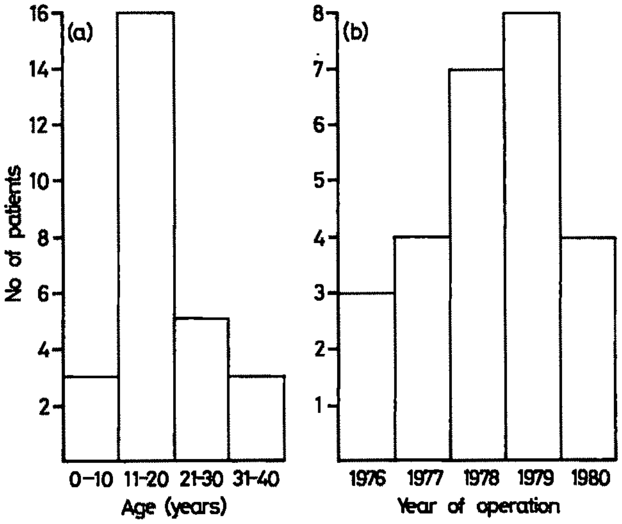

Fig. 2 *The age of patients (a) and the number of patients operated on in each calendar year 1976 to 1980 (b).*

since the previous operation. All were in sinus rhythm.

Other congenital cardiovascular anomalies were present or already treated in 10 patients. These were; coarctation (two), ventricular septal defect (two), atrial septal defect (one), persistent duct (one), mild pulmonary stenosis (one), left pulmonary artery stenosis (one), double left coronary orifice (one), and mild/moderate mitral regurgitation (five).

In 11 a myotomy was performed, with additional wedge resection of muscle from the massively hypertrophied ventricular septum in nine. One (case 13) had mitral annuloplasty for moderate mitral regurgitation and another (case 23) had repair of a cleft in the mitral valve and closure of a residual ventricular septal defect. One permanent pacemaker was implanted with epicardial leads (case 14) and a large duct was sectioned in case 2 after the aortic root replacement.

Results

DEATHS

One patient (case 3), aged 12 years, with tunnel obstruction and anomalous mitral papillary muscle attachment contributing to the obstruction died 48 hours after operation. This papillary muscle could not be excised because chordae were attached along its length, though after a difficult operation (bypass time two hours) the heart came off bypass easily with intermittent atrioventricular block, and there was no residual gradient across the left ventricular outflow tract. He died from left ventricular failure without evidence of valve dysfunction or coronary obstruction.

One late death (case 2) occurred among the 25 survivors at 37 months from the effects of progressive pulmonary hypertension related to the duct closure. This girl's aortic valve function was perfect and at catheterisation one month after operation no resting gradient was present across the competent aortic valve. At the time of operation, after valve replacement, it was noted that the pulmonary artery pressure was 88/50 mmHg when the systemic pressure was 120/85 mmHg and so the duct was closed. She was an example of the patient with the infantile type of left ventricular outflow obstruction with lumpy aortic valve stenosis and left ventricular disease, who had survived infancy probably because the duct had remained open, allowing shunt reversal and preventing the manifestations and inevitable effects of early left ventricular failure. Clearly the prognosis of the patient would have been better if the duct had been left open.

COMPLICATIONS

One patient (case 8) required five days of balloon counterpulsation after vein grafts to the left anterior descending and marginal branch of the circumflex coronary arteries. She is well, three years later, leading a normal life with a normal electrocardiogram and no residual signs of aortic stenosis. Three patients (cases 4, 18, 25) required insertion of permanent pacing systems four, 11, and 14 days after operation because of complete heart block. On the second postoperative day one patient (case 7) had a *grand mal* seizure with episodes of ventricular fibrillation and ventricular tachycardia. Emergency aortic root and valve replacement had been performed because of active bacterial endocarditis; three years later he is free of symptoms with no signs of aortic valve abnormality.

FOLLOW-UP

The exact status of 22 of the 24 survivors is known to date. Two have not been seen at the National Heart Hospital since discharge after operation; one (case 13) returned to Mauritius and has been seen on television playing football and the other (case 21) refuses to attend as she considers herself normal. She is reported to have no murmurs.

The other 22 patients were free of symptoms and living normal lives one to five years later. None had signs of aortic stenosis. Trivial angiographic aortic regurgitation which was present in four was not audible in any.

New left bundle-branch block appeared in one patient (case 16) immediately after operation and was already present in another. The electrocardiogram showed a reduction in left ventricular hypertrophy in 13 patients, and in five patients the grade of left ventricular hypertrophy remained unchanged. The four patients with permanent pacemakers were pacing satisfactorily and leading normal lives.

Calcification in the homograft aortic walls developed in three aged 7 to 11 years (Fig. 3). The aortic valve cusps were not calcified and continued to show clear opening and closing sounds (see phonocardiogram beneath Fig. 7).

Long-term anticoagulants were not used. Routine prophylaxis for all dental manipulations was advised.

POSTOPERATIVE INVESTIGATION

Cardiac catheterisation was performed in 16 patients, three weeks to 21 months after operation. Two patients had two studies, one three weeks and 14 months and the other five weeks and eight months after operation. The resting gradients across the left ventricular outflow tract were 0 to 33 mmHg in the 16; all were subvalvar and there were no gradients across the valve (Fig. 4). Nine patients with resting gradients of 0 to 33 mmHg were given isoprenaline which increased the gradients to 33 to 105 mmHg in

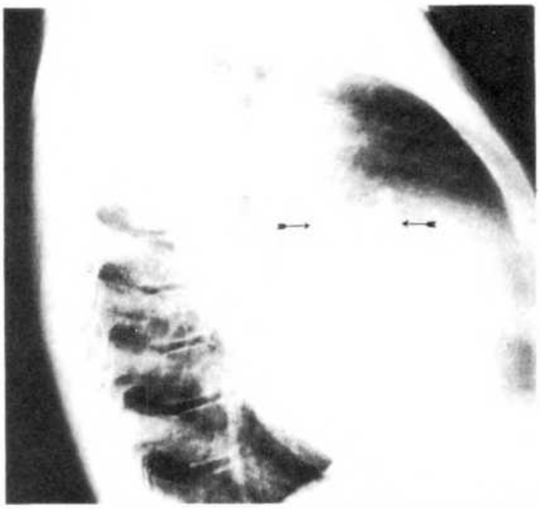

Fig. 3 *Lateral chest radiograph from case 2 two years after aortic homograft root and valve replacement showing calcification of aortic wall of the graft root (arrows) which did not involve the aortic cusps.*

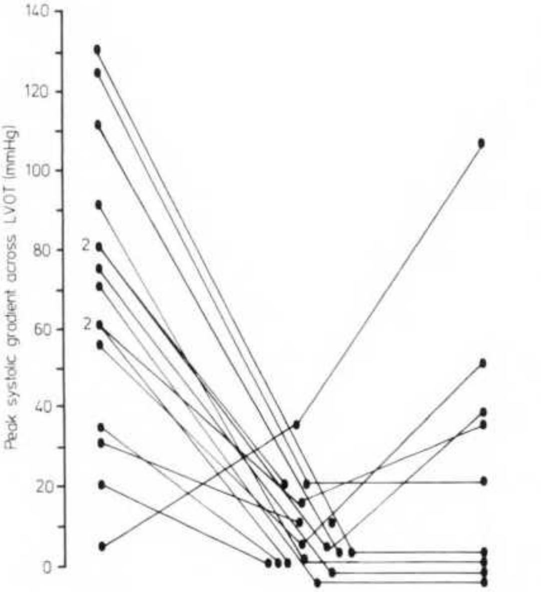

Fig. 4 *Peak systolic gradients across the left ventricular outflow tract in 15 patients before operation at rest (one dot represents two patients marked by a 2), at the first postoperative investigation at rest (16 patients, one of whom had no preoperative investigation), and after isoprenaline (nine patients). Seven patients were not given isoprenaline.*

four but did not change them in five. The boy (case 26) with a stimulated gradient of 105 mmHg had very severe septal bulging and irregular hypertrophy of left ventricular muscle; his first operation was for supra-aortic stenosis and he had no gradient before the second operation for aortic regurgitation precipitated by sudden cusp avulsion. The restoration of a competent aortic valve in the presence of severe septal hypertrophy may allow stimulated gradients to occur but it is to be hoped these will disappear as the hypertrophy regresses.

Aortography showed normal looking roots with coronary orifices and arteries well filled in 15 of the 16 patients (Fig. 5a and b). In case 2 the left coronary artery had been repaired at operation and was not seen. The left ventricular outflow seemed to have increased in size and appeared anatomically more normal than before operation (Fig. 6a and b).

The clinical state of the nine patients who have not had postoperative invasive investigation and the reasons they have not been restudied are summarised (Table 2). Two dimensional echocardiography in seven of the nine not invasively investigated and 11 of the 16 restudied patients showed no outflow obstruction, a normally opening aortic valve, and no fluttering of either the aortic or mitral valves. The aortic root appeared slightly thickened in some and normal in others. M-mode echocardiogram showed normal left ventricular cavities and function with a central normal closure line of the homograft aortic valve (Fig. 7a and b). No patient has had endocarditis since operation.

Discussion

Tunnel left ventricular outflow obstruction may be present when the patient first presents or it may develop with supra-aortic, fixed subaortic, or valvar obstruction, particularly when incomplete relief of the obstruction has been achieved earlier in childhood. Some centres regard tunnel obstruction as being a long subvalvar obstruction, but we consider that it may be part of much more diffuse pathology involving the ascending aorta, often pathologically abnormal, and the annulus. In our experience this problem does not appear when significant aortic regurgitation is produced at the first operation. Though aortic regurgitation may precipitate the need for earlier reoperation it may be better than persistent obstruction since the difficulties posed by a tunnel narrowing are not present. If sudden late aortic regurgitation occurs, as in case 26 who developed cusp avulsion, the tunnel obstruction will remain and produce severe left ventricular failure. Whatever the initial cause of their left ventricular obstruction, patients who acquire tunnel obstruction have diffuse congenital cardiovascular

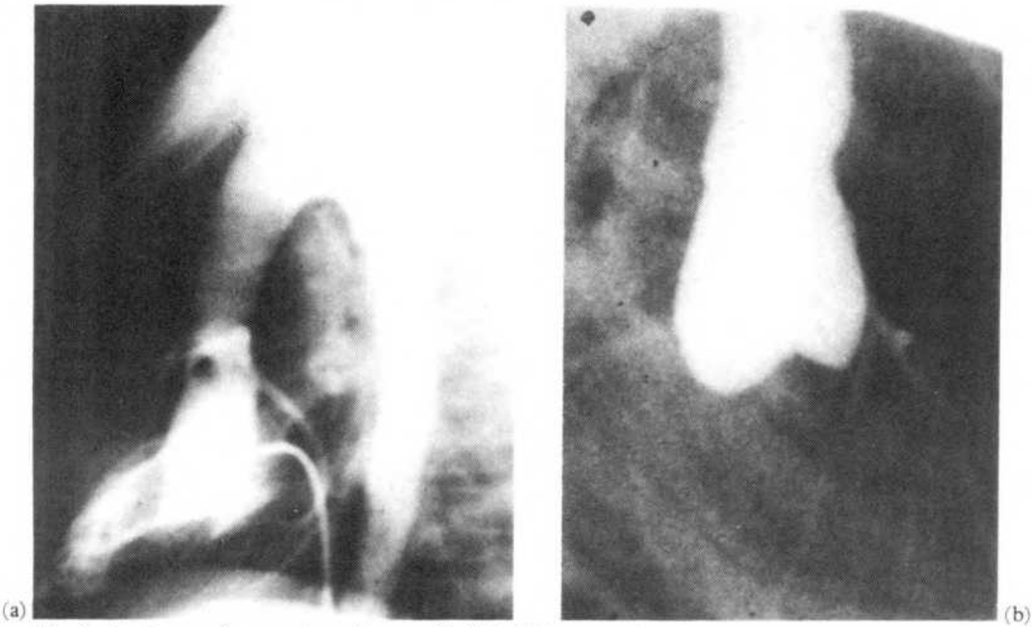

Fig. 5 *Angiograms from case 1, an 11-year-old child with lumpy aortic valve stenosis and diffuse tunnel obstruction found at operation but not easily seen in this angiographic view. (a) Left ventricular angiogram—lateral view before operation. (b) Aortogram six months after aortic root and valve replacement by aortic homograft. The aortic valve was competent and looked normal. Both coronary arteries filled normally.*

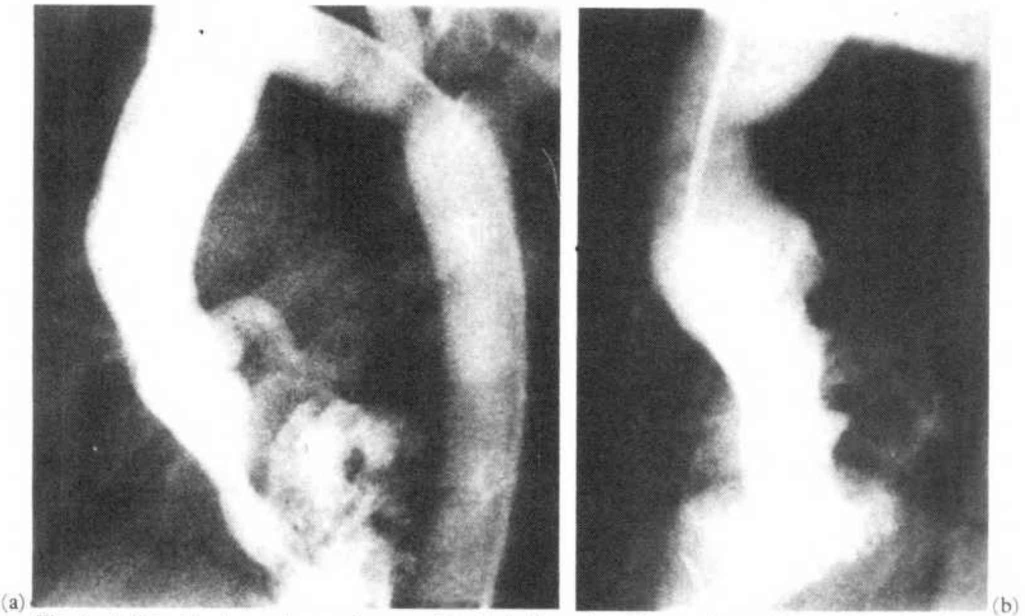

Fig. 6 *Left ventricular angiograms from case 18 who had resection of coarctation aged 1 month, open aortic valvotomy aged 5 years, and presented at the age of 8 years with severe aortic valve stenosis and tunnel obstruction. (a) Before aortic root and valve replacement showing small aortic root and ascending aorta, and diffuse narrowing of subvalvar region. (b) Seven months after operation. Aortic root and valve now look normal. The tunnel narrowing is no longer visible though septal bulging remains. The distal suture line of the aortic graft appears slightly thickened. There was no gradient between the left ventricular body and ascending aorta at rest or with isoprenaline stimulation.*

Table 2 *Summary of nine patients who have not had postoperative investigation*

Case No.	*Symptoms*	*Electrocardiogram*	*Problems*	*AR*	*Reason for refusal*	*Follow-up time (y)*	*State*
4	—	CHB	Pacemaker	—	Patient	4	N
7	—	ISQ	—	—	Patient	4	N
10	—	Improved	—	—	Physician	3	N
13	—	?	—	?	Patient in Mauritius	2	N
17	—	Improved	—	—	Patient	2	N
21	—	?	—	?	Patient	2	N
22	—	LBBB	—	—	Physician	1	N
23	—	ISQ	—	—	Inadvisable	1	N
25	—	CHB	Pacemaker	—	Physician	1	N

AR, aortic regurgitation; CHB, complete heart block; LBBB, left bundle-branch block; ISQ, unchanged; N, normal; Patient, patient refuses; Physician, referring cardiologist refuses.

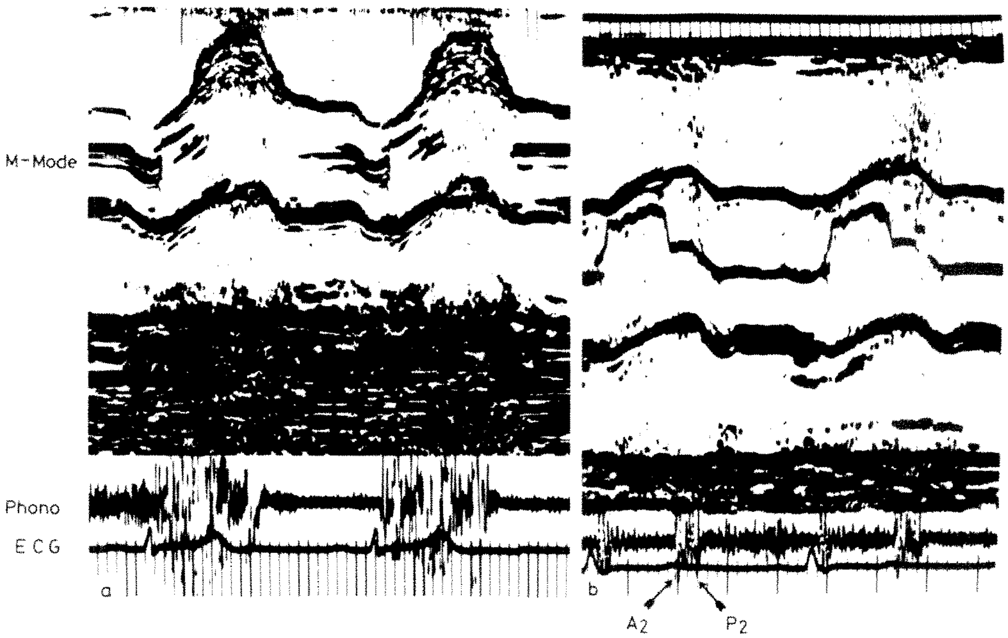

Fig. 7 *M-mode echocardiogram and phonocardiogram from case 11 with aortic valve stenosis. (a) Before operation. This shows thickened aortic valve with central abnormal opening and closure. (b) After homograft aortic root and valve replacement with normal opening of pliable normal aortic valve cusps. The intense systolic murmur has disappeared and aortic valve closure (A2) is clear and normal.*

abnormality[6] and can be recognised before the first operation.

Tunnel obstruction is difficult to relieve by the conventional replacement or repair operations for congenital aortic stenosis. Various techniques have been tried such as leaving the lesion in situ and adding a further anomaly in the form of an apico-aortic conduit ("Texas tube")[7] or transecting the ventricular septum (Konno) and inserting a prosthetic valve replacement.[8 9] Both provide relief of the obstruction but long term follow-up is unknown and additional anomalies added to the heart are the price of relieving the haemodynamic problem. The speed of degeneration in the valves or conduits used will greatly influence the late results. Glowing reports of a low mortality may make these other procedures sound attractive but the results should be correctly judged by the long term follow-up and complications in such a young group of patients.

Fresh aortic homografts have proved to be a good substitute for the diseased aortic valve and do not require anticoagulant therapy.[10-12] These are ideal for young patients and particularly women of child bearing age. Valve replacement alone, however, is often inadequate to relieve the outflow obstruction in these tunnel obstructions and is difficult to site in the small root. Once the root is excised the picture changes because the whole area opens widely enough to accept an adult sized graft in patients over 5 years of age.

Though this is a more complex procedure than a valve replacement it provides complete relief of the dynamic problems. We feel it is justified as the main aim of surgical treatment in congenital aortic stenosis is to produce or preserve normal left ventricular function. Inevitably, problems are likely to arise during the learning phase of any new surgical venture. Their recognition and solution is preferable to a denial of the value of a procedure because of early morbidity and mortality. Operative morbidity has been related to two problems: the siting of the coronary vessels and trauma to the conducting tissue.

Early in the series it was recognised that a patient would come off bypass easily but would develop deteriorating left ventricular function as the systemic pressure rose. It was clear that the left coronary artery flow was compromised but careful examination on bypass at first failed to demonstrate a cause. It became apparent that the difficulty was the result of tension on the left coronary artery which was stretched by the distended adult sized aortic sinus to meet the orifice of a much bigger adult aortic root homograft. Coronary grafts were necessary to salvage this situation. In all subsequent cases, free mobilisation of the left coronary artery has prevented this complication. Case 26 had a coronary graft as a prophylactic measure, as initially left ventricular function appeared compromised. Subsequent angiography confirmed coronary artery patency with normal flow.

Another important technical development has been to attach only the left coronary artery and then complete the upper homograft anastomosis. As the aorta becomes distended it becomes clear where the most appropriate site for anastomosis of the right coronary lies. This site may not coincide with the position of the right coronary orifice on the homograft. The left coronary orifice position, on the other hand, is usually constant at the mid-point of the left coronary sinus. The position of the right coronary artery is notoriously inconstant and this technique prevents malpositioning of the right coronary anastomosis.

Heart block was distressingly common at first but has only occurred once in the last eight patiens—a girl having her third operation. The cause was too low an excision of the root in the region of the membranous septum between the right and non-coronary cusps or the subsequent placing of attaching sutures. This complication can be avoided by attention to the vulnerable segment of ventricular septum.

As yet, in the short period of follow-up of one to five years, there have been no other complications and no evidence of progressive damage to the conducting tissue or the coronary arteries. The valves presumably, like other homografts and autografts, must be liable to infective endocarditis and thus the patients should receive careful advice about prophylaxis, though this complication had not in fact occurred. Another hazard of a tissue valve is that it may be infected at the time of insertion when sterilised in antibiotic solutions, but this is now extremely rare in our laboratory. A greater problem is the availability of material which may prevent many centres using this technique.

Calcification occurs sooner or later in all biological graft material whether homograft, xenograft, dura mater, pericardium, or fascia lata. Experience of aortic valves on the right and left side of the heart shows that it occurs early in the graft aortic wall but only exceptionally affects the cusps during the first decade of follow-up. In patients under 10 years it was radiologically apparent by the end of the second year but the cusps remained pliable, opening and closing normally without regurgitation, and the coronary orifices are widely patent. The long-term record of homografts, however imperfect, is far superior to that of xenografts, pericardial valves, and dura mater in younger patients.

It is accepted that a further operation will be needed eventually as with any valve replacement. If the homograft valve and root behaves as it does after right ventricular outflow tract reconstruction in patients from the same age group then it should not be required until the second decade of follow-up. The technical problems this will involve have yet to be discovered. Since a disc of native aorta has been left around the coronary orifices, they should not become obstructed.

Clearly this operation provides excellent relief of fixed and dynamic obstruction. Its use has been extended to other forms of aortic valve and root disease such as severe aortic regurgitation and ring destruction by infection where it is difficult to site a conventional homograft or autograft.

In view of these results it is now our policy to use this technique for all tunnel obstructions with small or diseased aortic roots. It is also indicated in those young patients with aortic regurgitation and important ring dilatation and in selected patients with active aortic valve endocarditis.

We are indebted to Susan Stone, research secretary, supported by an anonymous donor, who collected and collated the information. We thank Dr A Rickards for allowing us access to the haemodynamic data from postoperative investigations, Dr Simon Rees for help in interpreting the angiograms, and Barbara Hyams for the surgical drawings.

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Prevalence of ischaemic heart disease and associations with serum lipoproteins in subjects aged 45 to 64 years

The Speedwell study

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SUMMARY A longitudinal study has been set up to examine the incidence of ischaemic heart disease and its associations with serum lipoproteins including high density lipoprotein cholesterol and its subfractions, certain haemostatic factors, and other "risk" factors. We report here on our pilot study findings.

Cross-sectional data were available on 283 men and 68 women aged 45 to 64 representing 85% of the available population randomly selected from the lists of 16 general practitioners.

Reproducibility of the measurements of total serum cholesterol, triglyceride, and low density lipoprotein cholesterol was acceptable. The reproducibility of some of the other serum lipid fractions, for example high density lipoprotein cholesterol, was less good, in part because of the small range of the values found for these components.

Univariate associations of physical and behavioural characteristics and serum lipoproteins of men and women, with and without ischaemic heart disease, disclosed small and statistically non-significant differences except for levels of blood pressure. In particular, there was no significant difference in mean levels of serum high density lipoprotein cholesterol between men with ischaemic heart disease (0·91 mmol/l) and men without it (0·94 mmol/l).

In examining our data for the determinants of serum high density lipoprotein cholesterol using a linear multiple regression model, sex, serum high density lipoprotein cholesterol, and very low density lipoprotein triglyceride were the major factors, each individually explaining about 7% of the variance of serum high density lipoprotein cholesterol levels. In addition, alcohol intake and obesity each explained a further 2% of the variance.

The experience of the pilot study has led to modifications in the collection of blood samples and the subsequent estimation of lipid fractions.

In 1975, Miller and Miller[1] published their hypothesis in which they suggested that reduced levels of plasma high density lipoprotein might accelerate the development of atherosclerosis and, in turn, ischaemic heart disease. We considered that the evidence marshalled for that paper, together with new data, was sufficient to justify the establishment in Bristol of a longitudinal study whose main objective would be the examination of the association of plasma high density lipoprotein cholesterol levels and the development subsequently of ischaemic heart disease.

In order to examine the feasibility of such a study, we have carried out a pilot study whose principal aims were to determine (a) the likely response rate, (b) the feasibility of collecting fasting samples of blood, and (c) the suitability of certain laboratory methods for the longitudinal study. We report here on the findings of the pilot study which includes only data on prevalent ischaemic heart disease. Since we began this study other workers have reported their findings on the association of plasma high density lipoprotein and incidence of ischaemic heart disease. In these centres high density lipoprotein data were already available,[2]

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or were obtained from deep frozen samples which had been collected two years previously.[3]

Patients and methods

The patients on the lists of 16 general practitioners based at two health centres serving adjoining areas of mixed social class were identified by age and sex and a random sample of 400 men and 100 women aged between 45 to 64 years was drawn. The reasons for choosing this number was that in men we wished to examine the levels of plasma high density lipoprotein in those with and without ischaemic heart disease. The expected lower prevalence of ischaemic heart disease in women would have necessitated a larger number of women to obtain estimates with reasonable precision, and we did not attempt this.

For both sexes we wished to examine the relation of high density lipoprotein to variables (other than ischaemic heart disease) such as low density lipoprotein cholesterol, very low density lipoprotein triglycerides, and obesity—data which would be available for every subject.

Subjects were asked to attend a local clinic where a history was obtained by questionnaire to determine a present or past history of ischaemic heart disease,[4] risk factors for this condition, and certain variables which are known to influence lipid metabolism. Subjects were measured for height, weight, and skinfold thickness, using standard anthropometric methods.[5] Casual blood pressure was measured in the left arm, using the Hawksley random zero instrument.[6] Diastolic blood pressure was recorded at the point of muffling (phase 4). A resting 12 lead electrocardiogram was recorded using a Mingograph 34 machine. Subjects were asked to attend the clinic again a few days later in the fasted state and venous blood samples were obtained with minimal stasis. They had been given instructions to avoid food and drink (apart from water) for a period of 14 hours before the venepuncture was due. In the case of shift workers or permanent night workers the appointment was arranged so that the fasting interval could be achieved.

Duplicate blood samples were taken from 10% of subjects to test the reproducibility of the measurements. Blood for lipid measurements was centrifuged 30 minutes after clotting at room temperature, and serum samples were transported in ice-water to the laboratory. Blood collection was delayed by an interval of two weeks for any subject with a recent history of minor illness, or by three months for a patient recovering from a major illness.

Lipoprotein lipids were quantified as follows (see Table 1): after addition of sodium dodecyl sulphate to an aliquot of serum, very low density lipoprotein was separated by centrifugation and the infranatant (containing low density lipoprotein and high density lipoprotein) was isolated by aspiration with a finely drawn out Pasteur pipette.[7] The very low density and the low density lipoprotein in a separate aliquot of serum were precipitated by addition of heparin and manganese chloride and sedimented by centrifugation.[8] The supernatant (containing high density lipoprotein) was removed and the precipitate discarded. Cholesterol and triglyceride in whole serum and in the fraction containing high and low density lipoprotein (that is the sodium dodecyl sulphate infranatant) and the cholesterol in the fraction containing high density lipoprotein (that is the heparin/Mn supernatant) were measured directly by enzymatic procedures (Boehringer–Mannheim; catalogue nos. 187313 and 166448) in a Technicon AutoAnalyzer II. Peak heights were measured visually and Precilip (Boehringer–Mannheim) was used for quality control. Disodium EDTA was added to the heparin/$MnCl_2$ supernatants to chelate excess Mn^{++} ions.[9] Very low density lipoprotein triglyceride was calculated as serum triglyceride minus (low plus high density lipoprotein) triglyceride, and low density lipoprotein cholesterol as (low plus high density lipoprotein) cholesterol minus high density lipoprotein cholesterol. When duplicate samples of serum

Table 1 *Summary of laboratory procedures and subsequent modifications for lipid estimations*

Sample	*Serum (1 ml)*	*Serum (2 ml)*	*Serum (2 ml)*
Procedure	Assayed directly for cholesterol and triglyceride (Technicon AAII/enzymatic)	Sodium dodecyl sulphate in 0·15 M NaCl added (final conc, 0·7% w/v)	Heparin and $MnCl_2$ added (final concs, 183 u/ml, 0·045 M)
		Incubated at 35°C for 2 h	Incubated at 4°C for 30 min
		Centrifuged	Centrifuged
		Supernatant (VLDL) discarded	Precipitate (VLDL plus LDL) discarded
		Infranatant (containing LDL and HDL) assayed for cholesterol and triglyceride (AAII)	Supernatant (containing HDL) assayed for cholesterol (AAII)
Modifications	EDTA-plasma used; centrifugal analyser used for both lipids	Preparative ultracentrifugation used to isolate VLDL	Final $MnCl_2$ conc increased to 0·09 M

LDL, low density lipoprotein; HDL, high density lipoprotein; VLDL, very low density lipoprotein.

were sent from the clinic, the laboratory workers were unaware of their identity.

Plasma glucose was measured by the automated glucose oxidase method of Trinder.[10]

The prevalence of ischaemic heart disease was estimated by three criteria: the presence of angina and a history of myocardial infarction using the standard WHO questionnaire for both,[4] and by electrocardiographic abnormalities. All electrocardiograms were classified by one observer using the Minnesota code[11] and subdivided into three groups: probable ischaemia (items 1–1, 1–2, 7–1); possible ischaemia (items 1–3, 4–1 to 4–3, 5–1 to 5–3); and no ischaemia (none of the above).[12]

Because of the small number of cases of ischaemic heart disease in the study, the univariate association of ischaemic heart disease with the various measurements has been recorded in this paper with all categories of ischaemic heart disease combined (any ischaemic heart disease), except in consideration of high density lipoprotein cholesterol. Univariate associations of each category of ischaemic heart disease and the above measurements have been determined but are not recorded in this paper. The determinants of high density lipoprotein cholesterol concentration have been considered using eight variables, viz, age, sex, obesity as weight/height^2,[13] alcohol consumption, smoking habit, a combined measure of physical activity at work and during leisure time, low density lipoprotein cholesterol, and very low density lipoprotein triglyceride. A multiple regression model was used to assess the association of each variate with high density lipoprotein cholesterol.

Table 2 *Study sample*

Population sample	*Men* 400	*Women* 100	*Total* 500
Moved away/not traced	71	16	87
Available population	329	84	413
Seen at clinic (1st visit)	285*	68	353
Returned for blood sample (2nd visit)	284*	68	352

*Includes two subjects who were discovered not to be aged 45 to 64 at the time the sample was drawn.

Table 3 *Reproducibility of lipid tests and plasma glucose duplicate pair analysis*

Test	*No. of pairs*	*Overall mean (mmol/l)*	*Coefficient of variation (%)*
Cholesterol			
Total	42	6·09	3·4
LDL	41	4·67	5·9
HDL	42	1·00	21·2
Triglyceride			
Total	42	1·50	11·0 (5·3)*
VLDL	41	0·61	29·2 (15·2)*
Plasma glucose	49	5·19	0·36

*Excluding one "rogue" pair with total triglyceride values of 2·65 and 4·00 and corresponding VLDL values of 1·07 and 2·47.

Results

The population drawn and seen by age and sex is shown in Table 2. After identifying 500 names from the lists of the doctors, 87 individuals could not be traced, leaving 413 potentially available subjects for the study. Of this number 353 were seen at the clinic where most of the data were obtained, and of these 352 returned in a fasted state for venepuncture, 284 men and 68 women. Two subjects (both male) were discovered to be outside the age range of the study. The data relating to these two individuals have been excluded leaving 282 male subjects for whom there were usable data. This represents an overall response rate of 85%.

Reproducibility of the biochemical measurements has been expressed as the coefficient of variation. Reproducibility for plasma glucose, total cholesterol and triglyceride, and low density lipoprotein cholesterol was acceptable and is shown in Table 3. Reproducibility of the remaining lipoprotein fractions, though more difficult to interpret, appeared to be less acceptable. The minimal recordable difference between pairs of samples for cholesterol was 0·1 mmol/l, which was 10% of the overall mean for high density lipoprotein cholesterol. Of 44 pairs of samples for high density lipoprotein cholesterol estimation, 17 had, in fact, differences of 0·1 mmol/l or less.

Table 4 *Prevalence of ischaemic heart disease in men and women by age*

	Ages of men (y)		*Ages of women (y)*	
	45 to 54	*55 to 64*	*45 to 54*	*55 to 64*
No. in sample	144	139	28	40
Angina	8 (6%)	14 (10%)	0 (0%)	4 (10%)
History of myocardial infarction	4 (3%)	11 (8%)	0 (0%)	4 (10%)
Ischaemia on electrocardiogram				
Probable	2 (1%)	6 (4%)	1 (4%)	1 (3%)
Possible	12 (8%)	14 (10%)	5 (18%)	4 (10%)
Any ischaemic heart disease*	23 (16%)	32 (23%)	6 (21%)	11 (28%)

*Note that the individual categories are not mutually exclusive and hence do not add up to the "any ischaemic heart disease" figure.

The prevalence of various categories of ischaemic heart disease is shown in Table 4. The individual categories of ischaemic heart disease were not mutually exclusive but there is little overlap of categories, especially in the younger age group. The prevalence of ischaemic heart disease in women was slightly higher than in men but the number of female cases is extremely small and these rates lack precision. In the rest of the tables data referring to ischaemic heart disease in women have not been given for this reason.

Univariate associations of physical and behavioural characteristics of the men and women and the presence and absence of ischaemic heart disease disclosed small and statistically non-significant differences apart from levels of blood pressure. In men, systolic and diastolic blood pressure levels were higher in those with ischaemic heart disease compared with levels in those without ischaemic heart disease (mean systolic blood pressure with ischaemic heart disease 160 mmHg (SD 30), without ischaemic heart disease 144 mmHg (SD 25); mean diastolic blood pressure with ischaemic heart disease 89 mmHg (SD 15), without ischaemic heart disease 85 mmHg (SD 13)). Differences between mean systolic and mean diastolic blood pressure with and without ischaemic heart disease were statistically significant ($p<0{\cdot}001$ and $p<0{\cdot}05$, respectively). Differences in the same direction for systolic and diastolic blood pressure levels in women were observed.

The associations between ischaemic heart disease and total cholesterol, total triglyceride, the lipoprotein lipids, and plasma glucose are shown in Table 5. The differences in concentrations of these lipids and lipoprotein fractions in men with and without ischaemic heart disease were small, and did not achieve statistical significance. Plasma glucose was higher in men with ischaemic heart disease (Table 5), but the difference from levels in those without ischaemic heart disease did not achieve statistical significance. The association of ischaemic heart disease and high density lipoprotein cholesterol concentrations was analysed further for two male age groups by each category of ischaemic heart disease—angina, history of myocardial infarction, and possible and probable electrocardiographic evidence of ischaemic heart disease. Differences in the concentration of high density lipoprotein cholesterol within these ischaemic heart disease categories for all age groups with and without evidence of the disease were small, inconsistent, and did not achieve statistical significance (Table 6).

Consideration of the eight variates singly as deter-

Table 5 *Serum lipid and lipoprotein concentrations and plasma glucose in men with and without ischaemic heart disease*

Variable	*No ischaemic heart disease*		*Any ischaemic heart disease*	
	No. of subjects	*Mean (SD) (mmol/l)*	*No. of subjects*	*Mean (SD) (mmol/l)*
Cholesterol				
Total	226	5·75 (0·96)	52	5·77 (0·93)
HDL	226	0·94 (0·43)	54	0·91 (0·46)
LDL	226	4·33 (1·00)	54	4·30 (0·95)
HDL/Total (%)	225	16·8 (8·1)	52	16·3 (8·3)
Triglycerides				
Total	226	1·55 (0·89)	52	1·66 (0·86)
VLDL	226	0·75 (0·64)	52	0·84 (0·70)
Plasma glucose	227	5·26 (1·39)	55	5·36 (0·98)

Note: Variation in numbers of subjects is explained by missing data.

Table 6 *Serum high density lipoprotein (HDL) cholesterol concentrations for men by age and category of ischaemic heart disease*

Ischaemic heart disease category	*45 to 54 years*		*55 to 64 years*		*45 to 64 years*	
	No. of subjects	*Mean HDL (SD)*	*No. of subjects*	*Mean HDL (SD)*	*No. of subjects*	*Mean HDL (SD)*
No angina	135	0·93 (0·43)	123	0·94 (0·44)	258	0·94 (0·44)
Angina	8	0·71 (0·21)	14	0·92 (0·50)	22	0·85 (0·43)
No history of myocardial infarction	139	0·93 (0·43)	126	0·94 (0·43)	265	0·93 (0·43)
History of myocardial infarction	4	0·65 (0·24)	11	0·98 (0·59)	15	0·89 (0·53)
No ischaemia on electrocardiogram	129	0·91 (0·42)	118	0·95 (0·43)	247	0·93 (0·43)
Possible ischaemia	12	1·00 (0·49)	13	0·94 (0·56)	25	0·97 (0·52)
Probable ischaemia	2	0·95 (0·50)	6	0·88 (0·51)	8	0·90 (0·47)
No ischaemic heart disease	120	0·93 (0·43)	106	0·94 (0·43)	226	0·94 (0·43)
Any ischaemic heart disease	23	0·87 (0·41)	31	0·94 (0·50)	54	0·91 (0·46)

Note: Any ischaemic heart disease=angina and/or history of myocardial infarction and/or possible or probable ischaemia on electrocardiogram. Data are *not* additive because one subject can have more than one of the individual ischaemic heart disease categories.

Table 7 *Serum high density lipoprotein (HDL) cholesterol concentrations and physical activity in men and women*

Physical activity	*Leisure activity*				*Work activity*			
	Men		*Women*		*Men*		*Women*	
	No.	*Mean HDL (SD) (mmol/l)*	*No.*	*Mean HDL (SD) (mmol/l)*	*No.*	*Mean HDL (SD) (mmol/l)*	*No.*	*Mean HDL (SD) (mmol/l)*
None					99	0·89 (0·40)	5	1·42 (0·61)
Light	148	0·90 (0·43)	45	1·24 (0·54)	70	0·88 (0·43)	30	1·20 (0·37)
Heavy	132	0·96 (0·44)	23	1·21 (0·41)	111	1·01 (0·46)	33	1·23 (0·58)
Total	280*	0·93 (0·43)	68	1·23 (0·50)	280*	0·93 (0·43)	68	1·23 (0·50)

*No data for two subjects of the original 282.

Table 8 *Serum high density lipoprotein (HDL) cholesterol concentrations and alcohol consumption in men and women*

Alcohol consumption (ml/wk)	*Men*		*Women*	
	No.	*Mean HDL (SD) (mmol/l)*	*No.*	*Mean HDL (SD) (mmol/l)*
0	20	0·81 (0·33)	17	1·04 (0·33)
1 to 49	124	0·91 (0·46)	34	1·17 (0·41)
50 to 99	46	0·95 (0·43)	13	1·65 (0·70)
100 to 199	37	0·98 (0·49)	4	1·23 (0·39)
200+	53	0·98 (0·37)	0	—
Total	280*	0·93 (0·43)	68	1·23 (0·50)

*See footnote to Table 7.

Table 9 *Serum high density lipoprotein (HDL) cholesterol concentrations and obesity index (weight/height^2) for men and women*

Obesity index	*Men*		*Women*	
	No.	*Mean HDL (SD) (mmol/l)*	*No.*	*Mean HDL (SD) (mmol/l)*
<20	14	1·09 (0·33)	4	1·38 (0·78)
20 to 21·9	27	1·19 (0·52)	12	1·18 (0·32)
22 to 23·9	41	0·84 (0·33)	12	1·17 (0·32)
24 to 25·9	79	1·02 (0·49)	13	1·49 (0·55)
26 to 27·9	63	0·87 (0·41)	15	1·20 (0·40)
28 to 29·9	37	0·84 (0·38)	2	0·85 (0·64)
≥30·0	19	0·68 (0·21)	9	0·88 (0·20)
Total	280*	0·93 (0·43)	67†	1·23 (0·50)

*See footnote to Table 7.
†No data for one subject of the original 68.

minants of high density lipoprotein cholesterol concentration for men and women showed no association with age or smoking habit. Exercise classified as light or heavy during leisure, and work activity classified as none, light, or heavy showed small positive associations with high density lipoprotein cholesterol concentrations in men, but small negative associations in women (Table 7). High density lipoprotein cholesterol levels rose with increasing alcohol intake in men and women (Table 8). As the index of obesity (weight/height^2) rose in men and women, high density lipoprotein cholesterol concentrations decreased (Table 9). Concentrations of high density lipoprotein cholesterol fell as low density lipoprotein cholesterol

Table 10 *Serum high density lipoprotein (HDL) and low density lipoprotein (LDL) cholesterol concentrations in men and women*

LDL (mmol/l)	*Men*		*Women*	
	No.	*Mean HDL (SD) (mmol/l)*	*No.*	*Mean HDL (SD) (mmol/l)*
<3·0	23	1·21 (0·63)	2	2·10 (0·71)
3·00 to 3·49	30	1·04 (0·44)	6	1·32 (0·37)
3·50 to 3·99	55	1·12 (0·53)	4	1·38 (0·34)
4·00 to 4·49	48	0·89 (0·36)	12	1·12 (0·36)
4·50 to 4·99	57	0·85 (0·28)	15	1·36 (0·69)
5·00 to 5·49	29	0·76 (0·15)	10	1·09 (0·31)
5·50+	38	0·71 (0·35)	19	1·12 (0·44)
Total	280*	0·93 (0·43)	68	1·23 (0·50)

Correlation coefficients—Men: $r = -0{\cdot}37$ $p<0{\cdot}01$; women: $r = -0{\cdot}24$ $p<0{\cdot}05$.
*See footnote to Table 7.

Table 11 *Serum high density lipoprotein (HDL) cholesterol concentrations and very low density lipoprotein (VLDL) triglyceride concentrations in men and women*

Triglyceride (mmol/l)	*Men*		*Women*	
	No.	*Mean HDL (SD) (mmol/l)*	*No.*	*Mean HDL (SD) (mmol/l)*
<0·2	46	1·14 (0·46)	23	1·38 (0·44)
0·2 to 0·39	44	1·02 (0·39)	17	1·32 (0·47)
0·4 to 0·59	43	1·04 (0·50)	6	1·12 (0·45)
0·6 to 0·79	39	0·88 (0·47)	9	1·26 (0·75)
0·8 to 0·99	33	0·99 (0·46)	4	0·83 (0·22)
1·0 to 1·49	37	0·68 (0·21)	9	0·90 (0·31)
1·5+	35	0·70 (0·22)	0	—
Not known	3	0·57 (0·21)	0	—
Total	280*	0·93 (0·43)	68	1·23 (0·50)

Correlation coefficients—Men: $r = -0{\cdot}32$ $p<0{\cdot}01$; women: $r = -0{\cdot}36$ $p<0{\cdot}01$.
*See footnote to Table 7.

and very low density lipoprotein triglyceride rose in men and women (Tables 10 and 11).

The eight variates were included in a multiple regression model with, as the dependent variables in turn, the high density lipoprotein cholesterol and the log high density lipoprotein cholesterol concentrations. It was found that the assumptions of the model were better satisfied by choosing the log values of high density lipoprotein cholesterol as the dependent variable. The full model explained 31·9% of the total variance of log high density lipoprotein cholesterol concentration. Sex, low density lipoprotein cholesterol, and very low density lipoprotein triglyceride were each significantly associated with high density lipoprotein cholesterol concentration ($p<0·001$). Each variate explained individually around 7% of the variance in high density lipoprotein cholesterol concentration. Alcohol and obesity index were also highly significantly associated with high density lipoprotein cholesterol concentration, with each variate explaining about 2% of the variance.

Age, smoking habit, and physical activity were not associated with high density lipoprotein cholesterol level using this model. A five variate model excluding these same three factors explained 31·7% of the total variance of log high density lipoprotein cholesterol concentrations.

Discussion

The feasibility of undertaking a longitudinal study of the associations between ischaemic heart disease and plasma lipids and lipoproteins was supported by the satisfactory response of those available within the population sample.

We were particularly encouraged by the willingness of our subjects to fast overnight and attend a clinic the following morning. We made this easier for our subjects by starting the clinic relatively early (7.15 am) and providing breakfast. In this way our subjects usually stopped off at the clinic on their way to work. Subjects who could not attend the clinic because they left for work before the clinic began were visited at home.

Reproducibilty of the lipid measurements was difficult to interpret because of the narrow range of values for some of the components. The coefficients of variation for high density lipoprotein cholesterol and very low density lipoprotein triglyceride were, however, sizeable, and were considered unacceptable for a longitudinal study. This has led to modifications in our methods, which include the use of Na_2 EDTA-plasma rather than serum, a reduction of the interval between venepuncture and lipoprotein quantification, the use of conventional preparative ultracentrifugation to isolate very low density lipoprotein, an increase in the final concentration of $MnCl_2$ (to 0·09 M) used for the very low density lipoprotein/low density lipoprotein precipitation,[14] and the measurement of lipid concentrations enzymatically in a centrifugal analyser (Table 1).

The prevalence of ischaemic heart disease in men was similar to that recorded by Reid and others in the Whitehall study using similar information from medical histories and electrocardiograms.[15] The overall prevalence (any ischaemic heart disease) for men in the Whitehall study was 11·3%, 17%, and 22·5% for men aged 40 to 49, 50 to 59, and 60 to 69 years, respectively.

The univariate associations of "risk" factors, including total cholesterol and triglyceride and the lipoproteins in particular, with ischaemic heart disease were not obvious except for blood pressure levels. Total cholesterol was marginally higher in those with ischaemic heart disease for both men and women. High density lipoprotein cholesterol was lower in men with ischaemic heart disease than in those without it. The ratio of high density lipoprotein/total cholesterol was marginally higher in men without ischaemic heart disease compared with men with it. The lack of clear association between these lipids and prevalent ischaemic heart disease is not unusual: for example the Framingham study showed no association between prevalence of ischaemic heart disease and total cholesterol.[16]

Because of the inverse associations of high density lipoprotein cholesterol and incidence of ischaemic heart disease reported from Framingham,[2] Tromso,[3] and Israel,[17] it was of interest to consider determinants of high density lipoprotein cholesterol levels from our data. The independent contributions of sex,[18–20] low density lipoprotein cholesterol,[21 22] very low density lipoprotein triglyceride,[19 21 23] alcohol,[24 25] and obesity[20 23] in explaining variations of high density lipoprotein cholesterol are in keeping with other studies.

Having established the feasibility of a prospective study, we are currently recruiting for long-term follow-up all men aged 45 to 59 years registered with the same 16 general practitioners using the improved laboratory procedures. In view of the existing evidence that ischaemic heart disease may be related more strongly to the concentration of high density $lipoprotein_2$[26] than to the other major high density lipoprotein $subfraction_3$, measurements of both subfractions are being made, using an ultracentrifugal microprocedure recently developed in our laboratory.[27]

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Haemostatic factors associated with ischaemic heart disease in men aged 45 to 64 years
The Speedwell study

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SUMMARY In the Speedwell study set up to examine primarily the relation of plasma lipids and ischaemic heart disease in men aged 45 to 64 years drawn randomly from the practices of 16 general practitioners, various haemostatic factors which may contribute both to thrombogenesis and atherogenesis were measured. Fibrinogen measured nephelometrically and plasma viscosity were positively associated with the prevalence of ischaemic heart disease. Antithrombin III was negatively associated with the prevalence of ischaemic heart disease. These associations were statistically significant at the 1% level of probability. Fibrinogen measured by a clotting method and the heparin neutralising activity of platelet poor plasma had negative and positive associations with ischaemic heart disease, respectively, but neither association achieved statistical significance. Because of the interrelation of these variables and also age, a multiple logistic regression analysis was undertaken separately for the two measures of fibrinogen. The negative association of "clottable" fibrinogen and the positive association of plasma viscosity with the prevalence of ischaemic heart disease were confirmed and both were statistically significant at the 5% level of probability. Apart from age the independent association of the other variables with ischaemic heart disease did not achieve statistical significance. Fibrinogen measured by both methods had positive and statistically significant associations with serum total cholesterol, but no associations with serum total triglycerides, smoking, or alcohol consumption. "Clottable" fibrinogen had an inverse and statistically insignificant association with serum high density lipoprotein cholesterol. The observed associations support the concept of the involvement of some haemostatic factors in the aetiology of ischaemic heart disease, and these associations are now being examined more critically in a longitudinal study.

In considering the aetiology of ischaemic heart disease it is necessary to study the elements of thrombogenesis as well as atherogenesis. Patients dying from myocardial infarction show evidence of coronary artery thrombosis, which antedates the infarction, as well as atheroma.[1 2] Other evidence indicates that substances in the blood which are thrombogenic may also be involved in the process of atherogenesis and arterial occlusion and thereby other clinical manifestations of ischaemic heart disease. Fibrin and platelets are present in mural thrombi and atherosclerotic plaques.[3–6] In developing plaques in the human aorta, Smith *et al.*[7] found increased concentrations of free low density lipoprotein and fibrinogen and in more advanced plaques high concentrations of the same lipoprotein bound to fibrin. Platelets may also aggregate and embolise causing myocardial damage and irritability[8 9]; or by the release of active substances alter arterial tone[10]; or contribute to atheroma formation.[11] At the same time, a number of elements exist, like antithrombin III, which can neutralise activated clotting factors and which may influence the extent of the above thrombotic and atherogenic processes. Finally, fibrinogen is also important in determining plasma viscosity and thereby influencing blood flow through occluding arteries.

Within the design of the Speedwell study[12] which is to examine longitudinally the relation between serum lipoproteins and ischaemic heart disease the feasibility

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of measuring some of these haemostatic factors was considered. Selection of the factors measured was influenced by the need to collect large numbers of blood specimens at a distance from laboratories as well as intra- and inter-subject variability of the individual factors. The results of the pilot study and the associations between the factors measured and prevalent ischaemic heart disease and other risk indications for ischaemic heart disease are reported.

Patients and methods

The design of the study has been described in the paper giving results of lipid and related measurements and ischaemic heart disease in the same population.[12] Venous blood samples were collected from men aged 45 to 64 years who were in a fasting state in the early morning. For subjects reporting minor illness, or major illness or surgery, blood samples were collected, respectively, two weeks or three months later. Fibrinogen was estimated by two different methods. "Clottable" fibrinogen (C) was measured in citrated plasma by the method of Clauss.[13] In the second method using EDTA plasma, fibrinogen (N) was measured by a heat precipitation nephelometric method.[14] Plasma viscosity was measured within a few hours of blood collection in the EDTA specimen using the method of Harkness.[15] Platelet count and haematocrit were determined by the Coulter S counter. Antithrombin III was measured biologically in serum by the method of von Kaulla[16] and immunologically by single radial immunodiffusion according to the method of Mancini *et al.*[17] The heparin neutralising activity of platelet poor plasma was measured using the heparin thrombin clotting time test.[18] The plasma response to thrombin was also monitored by a dilute thrombin clotting time test.[18] Estimations of platelet aggregation response to dilutions of adenosine diphosphate were carried out turbidometrically on citrated platelet rich plasma within two hours of collection. Within the four dilutions of adenosine diphosphate used we were unable to obtain consistent patterns of aggregation with which to quantify the responses of subjects and relate them to the prevalence of ischaemic heart disease. These estimations were discarded. Determination of the prevalence of ischaemic heart disease and other "risk factors" has been described in the paper giving results for the lipid analysis.

Results

Reproducibility of measurements was estimated from split specimens of blood taken from a subsample of subjects. Expressed as coefficients of variation, the estimations of reproducibility are shown in Table 1.

Table 1 *Reproducibility—duplicate pair analysis*

Test	*No. of pairs*	*Overall mean*	*Coefficient of variation (%)*
Fibrinogen			
Clottable (g/l)	46	2·97	7·5
Nephelometric (g/l)	46	4·20	6·0
Viscosity (centipoises)	47	1·65	1·8
Thrombin clotting time (s)	46	17·4	6·1
Heparin thrombin clotting time (s)	46	31·1	14·1
Antithrombin III			
Biological (s)	44	37·5	27·8
Immunological (g/l)	44	0·22	11·6
Platelet count (10^9/l)	47	184 000	8·2
Haematocrit (%)	47	0·45	2·5

Reproducibility of all measurements was acceptable except for the "biological assay" of antithrombin III by the von Kaulla method.

Mean values for the various factors measured for the population divided into those with "any" evidence of ischaemic heart disease by history and electrocardiogram and those without any such evidence are shown in Table 2. The variables for which the difference between those with and without ischaemic heart disease reached statistical significance were fibrinogen (N), plasma viscosity, and antithrombin III by immunological assay. While fibrinogen (N) levels were higher in men with ischaemic heart disease, fibrinogen (C) was higher in men without ischaemic heart disease. Antithrombin III activity estimated by the von Kaulla test gave differences for men with and without ischaemic heart disease in the same direction as that measured immunologically, but the differences were not statistically significant. The thrombin clotting times were similar in men with and without evidence of ischaemic heart disease. The heparin thrombin clotting times were shorter in men with ischaemic heart disease, indicating increased heparin neutralising activity (Table 3).

Interrelations existed between age, fibrinogen measured by both methods, heparin thrombin clotting times, viscosity, and antithrombin III as shown in the correlation matrix in Table 4. As fibrinogen has heparin neutralising activity and contributes significantly to plasma viscosity, a multiple logistic regression analysis was performed to see which if any of these variates (excluding antithrombin III) were independently associated with ischaemic heart disease. The regression was performed twice—one model included fibrinogen (N) and the second model included fibrinogen (C). Table 5 shows the regression coefficients for both models expressed in standard units. These units show the change in the logit of risk for one standard deviation change in the variable and allow for easier comparison of the relative importance of the independent variables. Age was an important predictor of ischaemic heart disease in both models and its positive associations were statistically

Table 2 *Association of ischaemic heart disease with haematological variables*

Variable	*No ischaemic heart disease*		*Any ischaemic heart disease*	
	No. of subjects	*Mean (SD)*	*No. of subjects*	*Mean (SD)*
Fibrinogen				
Clottable (g/l)	226	2·97 (0·63)	55	2·87 (0·61)
Nephelometric (g/l)	223	4·02 (0·93)	53	4·39 (0·85)*
Viscosity (centipoises)	223	1·64 (0·09)	53	1·69 (0·10)*
Platelet count (10^9/l)	221	184 (54)	52	188 (51)
Haematocrit	225	0·455 (0·03)	54	0·448 (0·04)
Antithrombin III				
Biological (s)	217	37·3 (17·1)	52	34·8 (16·8)
Immunological (g/l)	217	0·23 (0·03)	54	0·21 (0·03)*

*p<0·01.

Table 3 *Association of ischaemic heart disease and heparin thrombin clotting test*

Variable	*No ischaemic heart disease*		*Any ischaemic heart disease*	
	No. of subjects	*Mean (SD)*	*No. of subjects*	*Mean (SD)*
Thrombin clotting test time (s)	223	17·4 (1·2)	54	17·6 (1·2)
Heparin thrombin clotting test time (s)	223	32·2 (10·0)	54	30·0 (8·8)

Table 4 *Haematological variables—correlation matrix*

	Age	*Fibrinogen (N)*	*Fibrinogen (C)*	*Viscosity*	*Heparin thrombin clotting time*	*Antithrombin III (i)*
Age	1					
Fibrinogen (N)	0·24***	1				
Fibrinogen (C)	0·09	0·40***	1			
Viscosity	0·20**	0·60***	0·35***	1		
Heparin thrombin clotting time	−0·12*	−0·40***	−0·46***	−0·35***	1	
Antithrombin III (i)	−0·19**	−0·14*	0·14*	−0·13*	0·09	1

Fibrinogen (N), nephelometric; Fibrinogen (C), clottable; Antithrombin III (i), immunological.
No. of subjects varies between 265 and 281.
*p<0·05, **p<0·01, ***p<0·001.

Table 5 *Multiple logistic regression coefficients for two models with different estimations of fibrinogen*

Variable	*Standardised regression coefficient (SE)*	*Variable*	*Standardised regression coefficient (SE)*
Age	0·365 (0·164)	Age	0·388 (0·166)
Fibrinogen (N)	0·068 (0·214)	Fibrinogen (C)	−0·513 (0·200)
Viscosity	0·336 (0·198)	Viscosity	0·497 (0·180)
Heparin thrombin clotting time	−0·045 (0·180)	Heparin thrombin clotting time	−0·262 (0·196)

Fibrinogen (N), nephelometric; Fibrinogen (C), clottable.

significant (p<0·05). In the model containing the variate of fibrinogen (C), both fibrinogen and viscosity showed moderate associations in opposite directions with ischaemic heart disease, and both associations were statistically significant (p<0·01). A moderate positive association of viscosity with ischaemic heart disease was shown also in the other model, but this association did not reach statistical significance at the 5% level of probability. The associations of fibrinogen measured by the two methods with ischaemic heart disease independent of the effect of age, viscosity, and heparin thrombin clotting times were in opposite directions. The heparin thrombin clotting times are negatively associated with ischaemic heart disease (that is positive associations for the heparin neutralising activity measured), but the associations in both models are not statistically significant at the 5% level.

Fibrinogen measured by both methods was positively associated with age (Table 4). Positive but weak associations with serum total cholesterol existed with both measures of fibrinogen (fibrinogen (N) $r=0{\cdot}15$, $p<0{\cdot}01$; fibrinogen (C) $r=0{\cdot}18$, $p<0{\cdot}01$). A negative but statistically insignificant association ($r=-0{\cdot}11$) existed between serum high density lipoprotein cholesterol and fibrinogen (C). No association was shown with fibrinogen (N) and high density lipoprotein cholesterol, or between either of the two measures of fibrinogen and serum total triglycerides. Fibrinogen (N) had a weak positive association ($r=0{\cdot}12$, $p<0{\cdot}05$) with the obesity index, weight-height^2. No associations with smoking habit or alcohol consumption were apparent with either measure of fibrinogen.

Plasma viscosity showed positive associations with serum total cholesterol ($r=0{\cdot}23$, $p<0{\cdot}001$) and serum total triglycerides ($r=0{\cdot}22$, $p<0{\cdot}001$). No further associations were shown for smoking, alcohol consumption, or obesity index with plasma viscosity, heparin thrombin clotting times, or antithrombin III. Antithrombin III measured immunologically had an inverse association with age (Table 4).

Discussion

The study was satisfactory in that 86% of the random samples of men gave fasting blood specimens on which the haemostatic factors were measured. The reproducibility of the measurements, except for the von Kaulla biological assay for antithrombin III, was acceptable. Estimations of platelet aggregation response to dilutions of adenosine diphosphate turbidometrically were inconsistent over the period of the study. Because of the difficulties of interpretation and quantification, this form of assessment of platelet aggregation seems unsuitable for large epidemiological studies.

The two different methods of measuring fibrinogen gave associations with the selected manifestations of ischaemic heart disease. It is not uncommon for measurements of different properties of proteins to have dissimilar associations with other variables. The correlation coefficient of the two measurements of fibrinogen was 0·40. Hampton *et al.*,[19] using a chemical estimation of fibrinogen, found higher mean levels and greater variability in levels on repeated samples in subjects with ischaemic heart disease than in subjects of similar age without a history or electrocardiographic evidence of ischaemic heart disease.[19] Pilgeram[20] using a method of estimation of fibrinogen which depends on its conversion to fibrin and spectrophotometric quantification of fibrin yield by ninhydrin found fibrinogen levels 20% higher in patients six months after myocardial infarction than in age matched controls. Meade *et al.*[21] have shown positive associations between prevalent ischaemic heart disease and clottable fibrinogen levels in men aged 40 to 64 and also increased fibrinogen levels in the same population of men who die from cardiovascular disease compared with those who survive over a mean 33 month follow up period. Further studies by Pilgeram[22] have indicated that raised fibrinogen in patients with coronary thrombosis is associated with an increased rate of biosynthesis and turnover of the molecule. There may also be defects in those patients' capacity to lyse fibrin.[22]

Fibrinogen measured by both methods was associated with age and serum total cholesterol, but not with smoking or alcohol consumption as in the studies by Meade *et al.*[23] and Korsan-Bengtsen *et al.*[24] The differences in association may relate to selective factors acting upon the populations studied as well as to differences in measurements. Fibrinogen in this study determined some of the variation in plasma viscosity. But plasma viscosity itself was shown to be independently and positively associated with ischaemic heart disease. Plasma viscosity was also positively associated with serum total cholesterol and total triglycerides. Plasma viscosity determined by fibrinogen, other proteins, lipids, and glucose will influence blood viscosity which is determined further by erythrocyte flexibility and mass.

The heparin neutralising activity of platelet poor plasma may be derived from a variety of sources. Heparin neutralising activity is raised after acute myocardial infarction and in the post-infarction state[25 26] and this rise relates, at least in part, to raised fibrinogen levels. When fibrinogen and other heat labile proteins are removed by heating platelet poor plasma, however, the heparin neutralising activity of the plasma remains raised in a proportion of cases of acute myocardial infarction and other thrombotic conditions.[27] Thus the heparin thrombin clotting time test must be considered as a non-specific measure of the heparin neutralising activity of a number of proteins in platelet poor plasma which have association with ischaemic heart disease.

Antithrombin III was measured in serum and represents residual levels after clotting. The lower levels of antithrombin III observed in subjects with ischaemic heart disease may represent lower preexisting plasma levels contributing to a prothrombotic state or increased usage during in vitro clotting of blood containing higher concentrations of thrombogenic substances.

In considering haemostatic factors in the aetiology of ischaemic heart disease it is realised that there are a large number of such factors which could be measured. Histological studies indicate the involvement of various factors like fibrinogen, fibrin, and platelets. But other work now indicates the importance of endothelial damage,[28] intraendothelial and intraplatelet prostaglandins,[10] other clotting factors,[21] and mechanisms that neutralise or lyse thrombotic factors[23] in the processes of thrombogenesis and atherogenesis. Generating and testing hypotheses with these large numbers of factors and mechanisms in epidemiological studies concerned with the aetiology of ischaemic heart disease will be exhausting of resources and public co-operation. The problem is being tackled by separate studies determining initially associations of ischaemic heart disease and its risk indicators with different factors and by the use of more global, non-specific tests like the heparin thrombin clotting times.[18]

The association of blood levels of the above factors with ischaemic heart disease does not necessarily imply causation, and their interpretation must be viewed with caution in cross-sectional studies in particular when only those subjects surviving ischaemic heart disease and other diseases are available. This study has shown both the feasibility of measuring some haemostatic factors in a random population and interesting associations with ischaemic heart disease and some of the established risk indicators. These factors, and others having associations with cardiovascular deaths in the Northwick Park heart study,[21] are now being measured in a large random sample of men aged 45 to 59 to determine their associations with the incidence of ischaemic heart disease.

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Haemodynamic effects of pregnancy in patients with heart failure

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SUMMARY Four patients, who were maintained on a constant regimen of treatment, developed congestive cardiac failure during pregnancy. They were examined regularly and carefully during the course of pregnancy to assess the progress of their failure. All four demonstrated unequivocal improvement during the third trimester attributable to obstruction of the inferior vena cava restricting venous return to the right side of the heart. This resulted in a fall in venous pressure in the neck and the resulting fall in right ventricular output could be very valuable in patients with left ventricular failure.

Cardiac output during pregnancy has been the subject of controversy over many years. There can be no doubt that it increases by as much as 30 to 50% but the main uncertainty centres around the timing of the ultimate decline towards the non-pregnant level. The available data are not adequate to resolve the controversy unequivocally but it is clear that during the third trimester the progressively enlarging uterus may compress the inferior vena cava, reducing the venous return to the heart and so the cardiac output. As a result, when the cardiac output is measured with the subject supine it gradually declines and at term is approximately at the non-pregnant level whereas if measured with the subject on her side it does not decline, or does so relatively little, until the puerperium.[1-3]

In the management of patients with heart disease during pregnancy the behaviour of the cardiac output is of crucial importance. An increase in venous return to the right ventricle may precipitate pulmonary oedema in a patient with an already raised left atrial pressure. Rational decisions about drug treatment and more particularly about the need for surgery are not possible without knowing whether to expect improvement or deterioration during the final 10 weeks. On the basis of those studies done in the lateral position, it is frequently stressed that clinical improvement cannot be anticipated in late pregnancy[4] and treatment should be planned on this basis. Our experience does not agree with this, and in the hope of throwing further light on this problem we present our findings in a small group of patients who were in cardiac failure during the course of pregnancy.

Subjects

Between 1976 and 1980 a special study was made of patients with signs of cardiac failure during pregnancy. The degree of failure was assessed solely by clinical examination, and this limitation demanded that certain criteria be fulfilled. Since isolated or dominant left ventricular failure cannot be quantified accurately by clinical means, it was necessary to include only those patients who had progressed to congestive failure with a definite and clearly visible rise in jugular venous pressure. There were nine such patients. One patient with a high jugular venous pressure caused by cor pulmonale was excluded from the study because of varying airways obstruction which caused frequent and irregular changes in pulmonary vascular resistance. A second patient was excluded because of atrial fibrillation with a rapid and variable ventricular response. A third case proved unacceptable because of thrombosis of a prosthetic valve shortly after 30 weeks gestation, giving a sustained rise in jugular venous pressure. Finally, two patients were excluded because their treatment was varied so much that no conclusion could be drawn as to the intrinsic circulatory state. The remaining four patients proved suitable for study. Three were admitted to hospital during the second trimester because of grade III dyspnoea (NYHA classification). At this stage they had pulmonary venous hypertension but their jugular venous pressure was still not above the

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normal range for pregnancy. From the time of admission they were maintained at rest in bed on a constant regimen of antifailure treatment. The fourth patient (case 4, Table), with moderate rise in jugular venous pressure and mild symptoms, was maintained on a constant drug regimen at home under stable conditions of a constant daily routine.

In all four cases, the jugular venous pressure was checked weekly with the patient sitting up in bed at a constant angle of 45 degrees. The venous pressure was taken as the top of the "v" wave of the internal jugular pulsation. It was classified as grade 0 where the venous pressure was so low that no pulsation was visible, grade 1 where the top of the pulsation was in the lower third of the neck, grade 2 where it was in the middle third, and grade 3 where it was in the upper third or higher. Grades 0 and 1 are normal during pregnancy.

Table *Jugular venous pressure during pregnancy*

Case	*Cardiac disease*	*Jugular venous pressure*	
		Maximum	*At term*
1	Triple valve prostheses	Grade 3	Grade 2
2	Mitral prosthesis	Grade 3	Grade 0
3	Mitral prosthesis	Grade 2	Grade 0
4	Mitral prosthesis	Grade 2	Grade 0

Results

During the early months of pregnancy, all four patients had a normal jugular venous pressure, but between 25 and 30 weeks two reached grade 2 and two grade 3 (see Table). During the last nine to 10 weeks, the pressure declined to normal in three cases and from a high grade 3 (up to the ear-lobes) to a low grade 2 in one case (case 1 in Table). In addition, in one patient a systolic murmur of functional tricuspid regurgitation disappeared at 38 weeks (case 3 in Table). In all patients symptoms improved *pari passu* with the improvement in signs.

Discussion

The findings noted here suggest that in practice patients with cardiac failure tend to improve during the final 10 weeks of pregnancy. On reflection this accords with previous experimental results. Pregnant women, like everybody else, lie neither on their backs nor on their sides all day. They spend about a third of their time in bed, turning from one position to another, while during the day, they stand, sit, recline, and take exercise with almost infinite variety. Clearly then, their cardiac outputs are very variable but since they spend a large portion of their time supine or sitting in postures producing some caval obstruction it can truly be said that the average cardiac output declines progressively during the third trimester. This would explain the findings in our study and the very special value of bed rest in the management of patients with left ventricular failure during the third trimester.

One possible disadvantage of such a regimen is the risk of venous thrombosis. The cases reported here were already on anticoagulants because of their prosthetic valves but otherwise heparin, administered subcutaneously as outlined by Bonnar,[5] would be appropriate prophylaxis against this complication.

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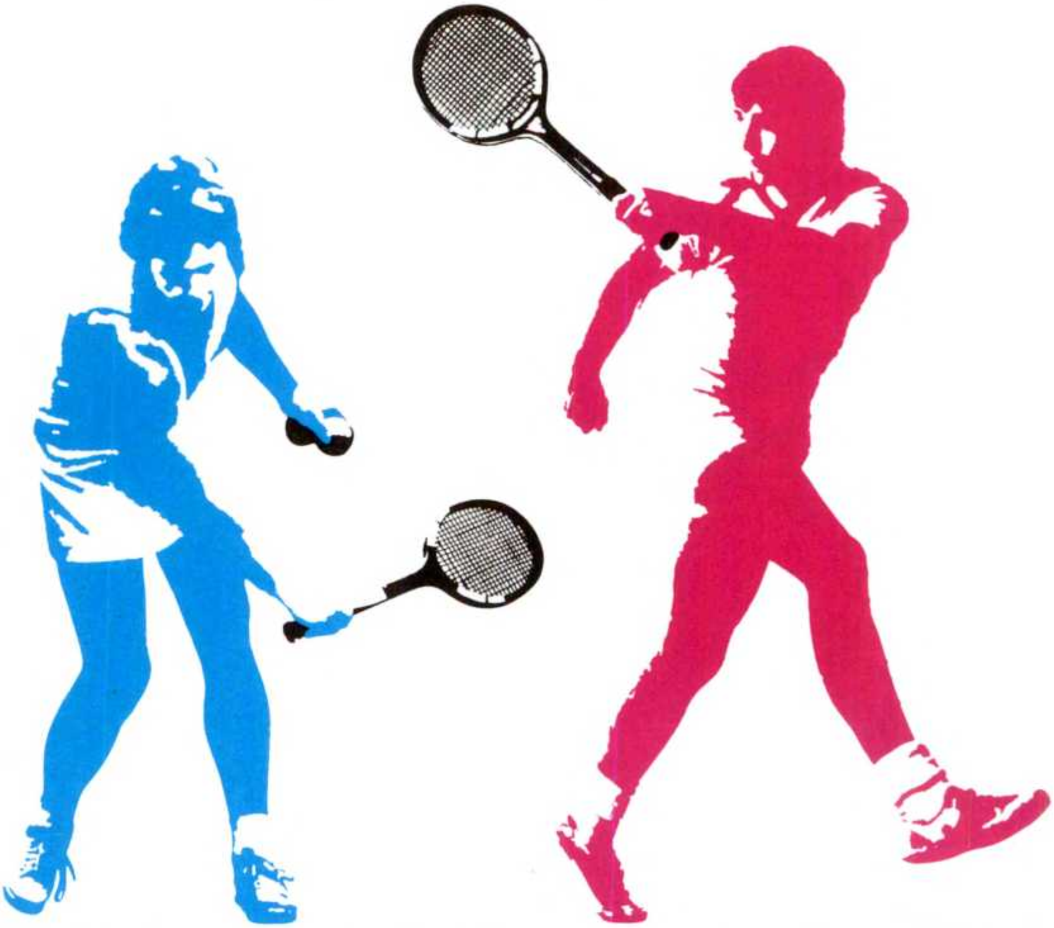

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Br Heart J 1982; **47**: 497–9

Constrictive pericarditis complicating an endocardial pacemaker

C J FOSTER

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SUMMARY A patient is described with constrictive pericarditis after insertion of an endocardial pacemaker. As far as we know this complication has not been reported previously.

Permanent endocardial pacemakers are now commonly implanted and a number of complications have been described.[1] Constrictive pericarditis has been reported as a complication of epicardial pacemakers[2]; this has never been reported, however, after insertion of an endocardial pacemaker.

Case report

A 62-year-old man was admitted with a three week history of episodic dizziness and effort dyspnoea. He had had mild hypertension for one year, but there was no history of any other cardiovascular disease.

On physical examination he had a heart rate of 35/minute, blood pressure of 235/90 mmHg, and a normal jugular venous pressure. The apex beat was mildly thrusting. On auscultation the heart sounds were normal and there was a grade 1/4 ejection systolic murmur in the aortic area.

The electrocardiogram showed 2:1 atrioventricular block and left anterior hemiblock with a ventricular rate of 35 a minute. Chest *x*-ray film showed moderate cardiomegaly.

A transvenous demand pacemaker was inserted via the left subclavian vein. The lead, a Lucas wedgeless tip model CLI-L-002, was easily positioned at the apex of the right ventricle (Fig. 1a), with no complications. He remained well until four weeks later when he developed dyspnoea, dry cough, and ankle oedema. Examination now showed a pyrexia of 38·5°C, and sinus tachycardia with a small volume pulse showing severe paradox. The jugular venous pressure was raised 8 cm with a large "a" wave. The heart sounds were now muffled and in addition there was a third heart sound with a pericardial friction rub at the left sternal border. The pacemaker was found to be working normally.

The electrocardiogram showed sinus tachycardia with left bundle-branch block; the chest *x*-ray film showed a pronounced increase in heart size and no change in position of the pacemaker lead (Fig. 1b). An echocardiogram confirmed the presence of a large

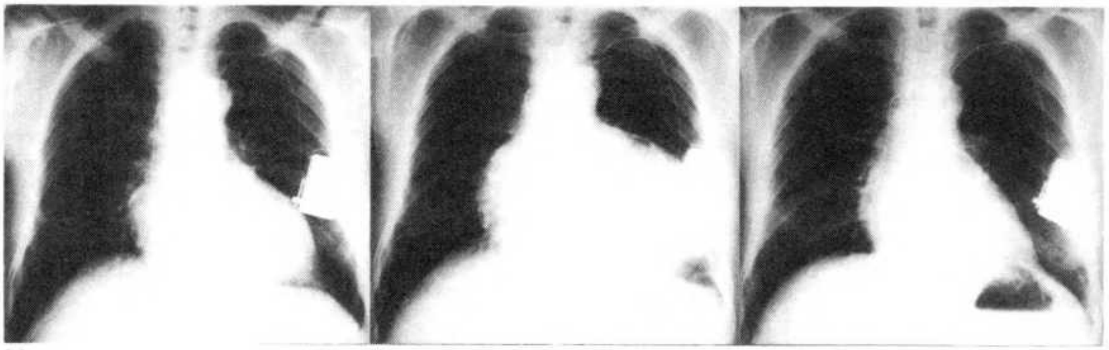
(a) (b) (c)

Fig. 1 *Series of chest x-rays. (a) Two days after pacemaker insertion showing moderate cardiomegaly (unchanged from before implantation) and good electrode position. (b) Two months later showing large pericardial effusion. (c) One year later showing decrease in heart size shortly before pericardectomy.*

pericardial effusion (Fig. 2a). Other investigations showed the following: Hb 10 g/dl, WBC 11·2, ESR 145 mm/hour (all previously normal). Antinuclear factor, cardiac antibodies, and viral studies were all negative.

Pericardial aspiration was performed with air replacement and limited right heart catheter studies (Table); 600 ml slightly bloodstained fluid was removed. Subsequent *x*-rays showed normal outline of the heart and pericardium. Examination of the pericardial fluid was sterile and negative for malignant cells. There were no acid-fast bacilli on staining and culture.

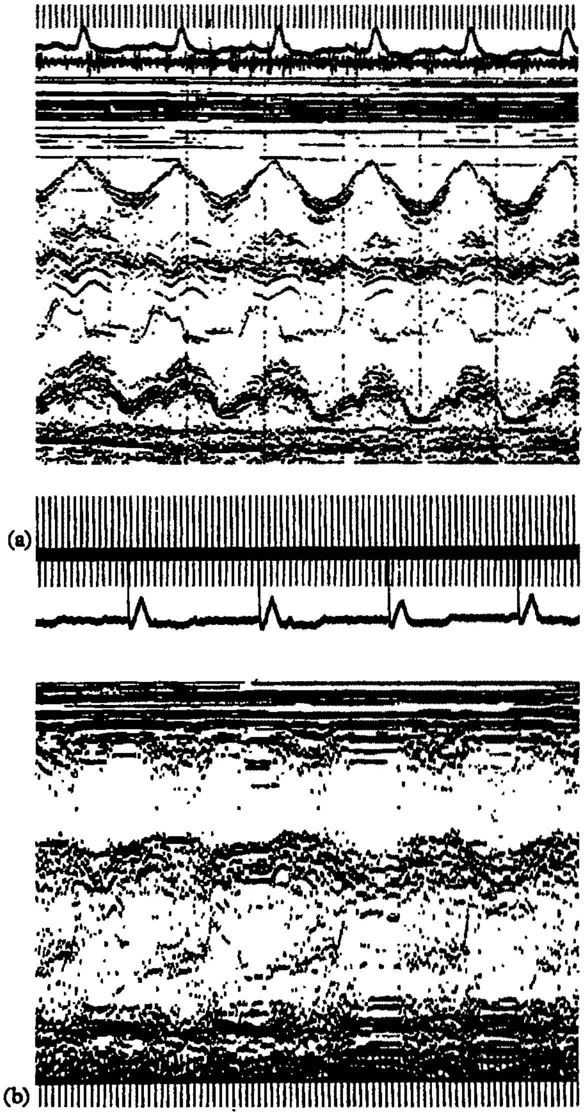

Fig. 2 *Echocardiograms. (a) Showing large pericardial effusion. (b) Complete resolution of effusion.*

On treatment with paracetamol and diuretics the patient's symptoms settled but the tachycardia and raised jugular venous pressure with tall "a" and steep "y" descent remained.

Ten months later he deteriorated, developing severe dyspnoea, orthopnoea, paroxysmal nocturnal dyspnoea, cough, and ankle oedema. The only new feature on examination was that the heart sounds were more muffled. The jugular venous pressure remained raised with a steep "y" descent.

The chest *x*-ray film showed an obvious reduction in heart size (Fig. 1c) and was now smaller than before pacemaker insertion. The echocardiogram showed no evidence of a pericardial effusion (Fig. 2b). Cardiac catheterisation (Table) showed a raised right atrial pressure with a steep "y" descent and equal right and left ventricular diastolic pressure with a prominent "dip and plateau" configuration (Fig. 3).

The left ventricular angiogram was normal and the right ventricular angiogram showed an abrupt termination of diastolic filling. Selective coronary arteriograms were normal.

At thoracotomy the pericardium was found to be thickened and densely adherent, especially over the inferior surface of the right ventricle, and was extensively excised. Histology showed fibrous tissue with focal lymphocytic infiltration. Culture was negative for *Mycobacterium tuberculosis*. He has since made a good recovery, with relief of his symptoms.

Discussion

Shortly after insertion of this patient's pacemaker he developed acute pericarditis with effusion and subacute tamponade.[3] He later developed pericarditis requiring pericardectomy.

Although it is possible that transient perforation of the right ventricular wall occurred at the time of

Table *Pressures taken before and after pericardiocentesis and at cardiac catheterisation*

	Pressures (mmHg)		
	Before pericardial aspiration	*After pericardial aspiration*	*At catheterisation*
RA mean	10	5	10
LA/wedge* mean	17*		13
RV	32/15		24/12
LV			120/13
Ao/RFA	140/86	165/95	122/78
Mean	103	125	100

*Pulmonary wedge pressure; at second catheterisation the pressure was direct left atrial.

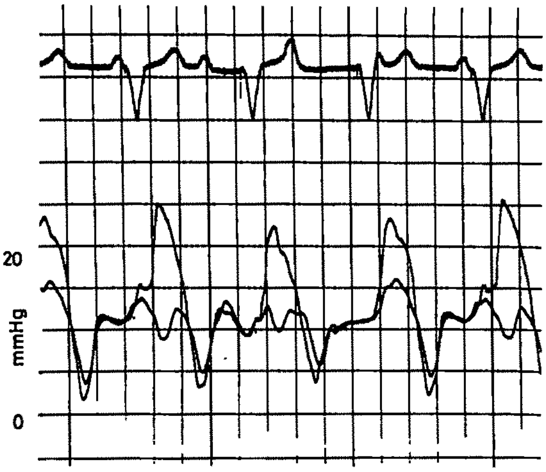

Fig. 3 *Simultaneous right atrial and right ventricular pressure traces at cardiac catheterisation showing typical "dip and plateau" configuration of constrictive pericarditis.*

implantation, there was never any evidence to suggest this, though it is thought to be a not infrequent occurrence. Perforation has been reported as causing acute tamponade[3] but there has been no report of severe pericarditis or pericardial constriction after suspected perforation.

Even though the cardiac antibodies in this case were negative it was felt likely that the acute illness was Dressler's syndrome. This was supported by the time of onset after pacemaker insertion, the physical findings, and the low Hb, raised white cell count, and raised erythrocyte sedimentation rate. The investigations did not indicate any alternative cause for the pericarditis and subsequent constriction. There has been one previous report of a case of Dressler's syndrome occurring after insertion of an endocardial pacemaker,[4] but this was not followed by any long-term complications. It is possible that if right ventricular perforation did occur the associated minor trauma to the myocardium could initiate Dressler's syndrome.

Constrictive pericarditis is unusual after Dressler's syndrome or the post-cardiotomy syndrome but it has been reported[5] and has been seen in this Unit (unpublished observation).

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Acute myocardial infarction and cerebrovascular accident in a young girl after a viper bite

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SUMMARY A 17-year-old girl developed an acute myocardial infarction immediately after being bitten by a viper and four days later she had a cerebrovascular accident. The close clinical and laboratory follow-up of this case suggested that myocardial damage could be attributed to a direct cardiotoxic effect of the venom, while the brain injury that subsequently appeared was probably the result of a disseminated intravascular coagulopathy, possibly in conjunction with vasculitis.

Acute myocardial infarction and/or ischaemia caused by snakebite has been reported a few times.[1 2] This injury was attributed to arterial thrombosis resulting from severe hypotension,[1] or to direct toxic effect of the venom on the myocardium.[2] In addition, emphasis was given to disseminated intravascular coagulation in cases of snakebite by the *Vipera echis carinatus*,[3] but toxic vasculitis was thought to be the main cause of haemorrhagic complications.[4] Neurological manifestations that constitute the predominant features in cobra bites were found in one-third of the cases with viper bites where bleeding and nephrotoxicity were encountered at higher rates.[4] Necropsy findings of subarachnoid and leptomeningeal haemorrhage as well as blood clot formation in the cerebral hemispheres have also been reported.[5]

The case of a 17-year-old girl who sustained successive injuries to heart and brain after a viper bite is presented, the sequence of these events suggesting that different mechanisms were involved.

Case report

On 23 July 1979, at about 6 00 am while working in a tobacco field in central Greece, a previously healthy 17-year-old girl was bitten on the inner aspect of the left big toe by a snake. The only poisonous snakes in this area are *Viperidae*, *Vipera berus* (adder), *Vipera ammodytes*, and *Vipera lepetina*, as is the case in the rest of the country.

Shortly after the bite the patient experienced severe substernal pain, nausea, and collapse. The local physician who saw the patient about half an hour later administered an antihistaminic compound intramuscularly, high doses of corticosteroids intravenously, and Pasteur antivenom subcutaneously. Four hours later the patient was admitted to the local hospital where the electrocardiogram showed paroxysmal atrial tachycardia at a rate of 180/min and pronounced ST elevation in leads II, III, aVF, as well as in leads V4 to V6 (Fig. 1A). Conversion of paroxysmal atrial tachycardia to regular sinus rhythm ensued after the intravenous administration of 5 mg verapamil. Frequent multifocal ventricular extrasystoles were interrupting the regular sinus rhythm, at times bursting into salvos. Atropine, given subcutaneously, increased the sinus rhythm and diminished the ventricular extrasystoles. The ST changes remained, however. At that stage the patient was transferred by helicopter to Athens and admitted to the coronary care unit of "Evangelismos" Hospital late in the afternoon of the same day.

On admission the patient was alert and coherent. Two fang marks were present at the inner aspect of the left big toe and the whole limb was swollen, cyanotic, and painful. On auscultation, tachycardia at a rate of 120/min and gallop were heard. The blood pressure was 120/70 mmHg. The electrocardiogram confirmed the previous findings but its monitoring showed no ventricular extrasystoles throughout the hospital course. As the ST became isoelectric, on the second day, Q waves appeared in leads II, III, aVF, along with T wave inversion in leads V3 to V6 (Fig. 1B). On the fourth hospital day the patient presented with right-sided hemiparesis and aphasia.

During the first six days in hospital she was given an intravenous drip of xylocaine 1 g in 1000 ml dextrose 5% in water, prednisolone 5 mg tid, heparin 5000 units every six hours intravenously, and thereafter dipyridamole 75 mg tid.

The laboratory follow-up (Table) showed a gradual

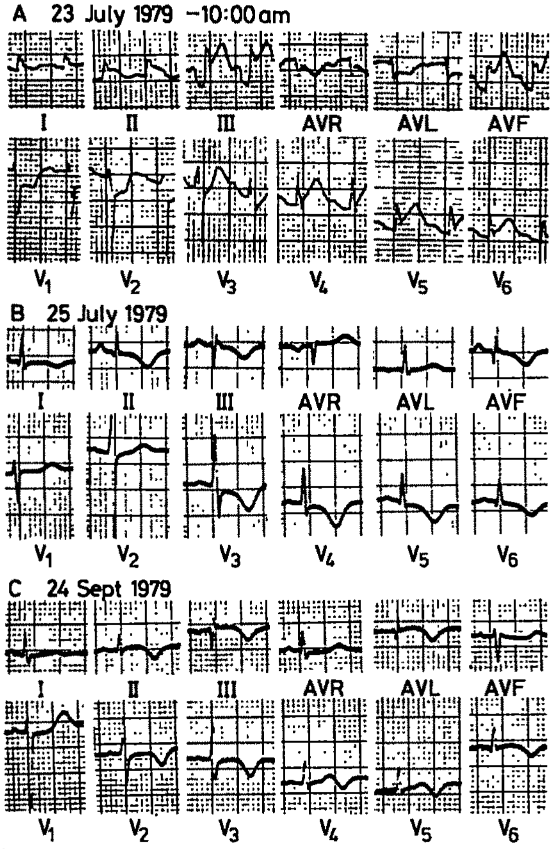

Fig. 1 *Electrocardiograms (A) four hours after the episode; (B) on the third hospital day; (C) two months after the episode.*

reduction in haematocrit from 42% on admission to 31% on the fifth day in hospital. The haemoglobin changes were similar. The platelet count from a low rate on admission returned to normal levels on the eleventh hospital day. White blood cell count showed an increase (14 500 per mm³) only on the third day, with 75% polymorphonucleocytes. Serum enzymes were raised on admission and they decreased to normal values on the sixth day except for lactic dehydrogenase which did so one day later. Serum bilirubin, total, direct, and indirect, showed a slight rise on admission and returned to normal levels after the third day. The sedimentation rate was within normal limits on admission and was moderately increased after the sixth day. More detailed haematological studies on the fourth day showed 3·7% reticulocytes, serum iron 14·7 mmol/l. Coombs test was negative. Prothrombin time (Quick's method) increased to 21 s (control 12·9 s), thrombin time to 17·1 s (control 12·1 s), Lee-White's test under heparin administration was prolonged to 28 s, partial thromboplastic time 69·8 s (control 63·3 s), and fibrinogen 5·16 g/l. Urinalyses showed albuminuria throughout the hospital stay and haemoglobinuria between the sixth and the ninth day. Liver function tests, blood sugar, blood urea nitrogen, electrolytes, serum protein electrophoresis, immunoglobins, and haptoglobulins were within normal limits. Chest x-ray film and fundoscopic examination were normal.

During the 19 days in hospital the patient showed slight improvement in her neurological functions and satisfactory progress of her heart condition.

Two months later she was readmitted for additional evaluation. Hemiparesis had subsided, and aphasia

Table *Haematological and biochemical data presenting changes*

Date (1979)	*24 July*	*25 July*	*27 July*	*28 July*	*4 August*	*9 August*
Haematocrit (%)	42	36	31	31	32	34
Haemoglobin (g/100 ml)	14·3	11·1	10·1	10·1	10·8	11·5
Platelets (mm³)	60 000	60 000	67 000	—	200 000	—
Reticulocytes (%)	—	2·4	3·7	—	—	—
White blood cells (per mm³)	9 000	14 500	8 350	7800	7 500	8000
Sedimentation rate (1st hour)	4	—	—	35	50	15
Lee–White's time (s)	28*	26*	—	—	—	—
Prothrombin time (s)	—	17 (12·1)	21 (12·9)	—	12·9 (12·8)	—
Thrombin time (s)	—	—	17·1 (12·1)	—	12·3 (12·2)	—
Partial thromboplastic time (s)	—	—	69·8 (63·3)	—	63·0 (63·2)	—
Fibrinogen (g/l)	—	—	5·16	—	—	—
Serum bilirubin (%)	1·0	—	0·9	0·8	0·4	—
Direct	0·4	—	0·4	0·3	0·2	—
Indirect	0·6	—	0·5	0·5	0·2	—
Serum enzymes (units)						
AST	122	132	40	20	10	—
AAT	47	68	62	28	27	—
LDH	630	—	920	200	—	—
CK	402	—	49	—	—	—

*Heparin 5000 units intravenously every six hours, —, no data available.
Numbers in parentheses denote control values.

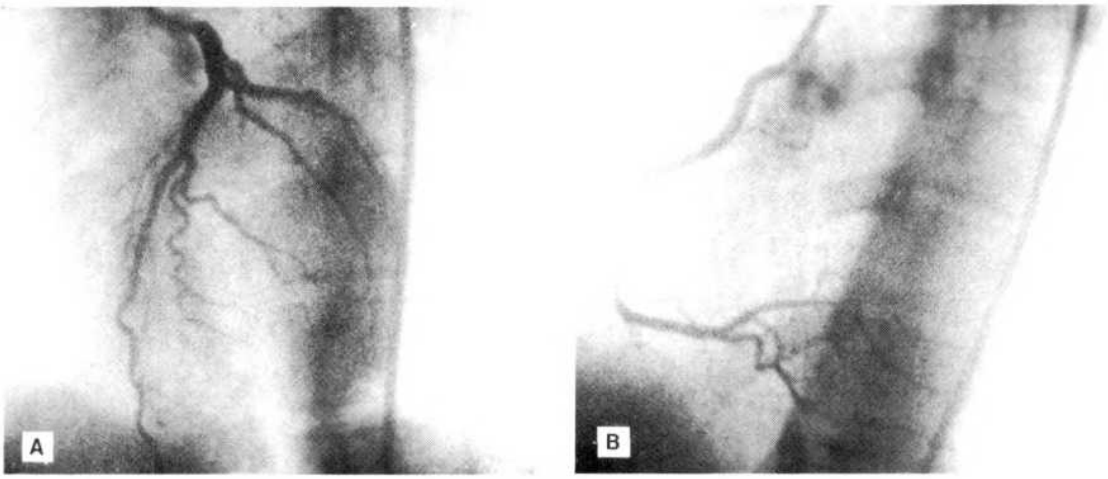

Fig. 2 *Coronary arteriogram. (A) left coronary artery; (B) right coronary artery.*

showed improvement. The electrocardiogram showed the picture of an old inferior wall myocardial infarction (Fig. 1C). A treadmill exercise test was performed at various levels and showed no abnormalities. The patient underwent cardiac catheterisation and coronary angiography. Catheterisation disclosed normal pressures, and coronary arteriography showed both coronary arteries and their branches to be patent throughout (Fig. 2A, B). The left ventriculogram showed decreased contractility of the posterior and inferior wall.

Discussion

As to the mechanism responsible for the myocardial infarction and the cerebrovascular damage in this patient one should consider the following factors: (a) direct toxic effect of the venom,[2] (b) shock,[1] (c) arterial obstruction occurring from ensuing thrombosis[3] or haemorrhage.[4]

The course of events in the myocardial incident suggests a direct toxic effect of the venom on myocardial tissue. Chest pain preceded the shock while the electrocardiographic evidence of acute myocardial ischaemia and ventricular irritability persisted long after recovery from shock. Specifically, shock might have been the result of the venom's cardiotoxic effect which, besides damaging the myocardium, seems to have triggered the initially observed paroxysmal atrial tachycardia. A direct toxic effect of cobra venom on the cat's myocardial tissue has been described by Kellaway and Trethewie[6] and a similar effect of viper venom has been suggested by Sarangi *et al.*[4]

Alternatively, it seems reasonable to suppose that prolonged hypotension along with haemolysis and a high fibrinogen could have contributed to the development of myocardial infarction. The absence of major arterial occlusion on coronary angiography performed about two months after the episode does not rule out the possibility of major thrombosis that might have cleared by that time, nor that multiple small vessel occlusions might have been present.

On the other hand, the brain damage observed almost four days after the viper bite was unlikely to be the result of the venom, nor could it be related to shock which was present in the very early stages only. It is, however, possible that despite intermittent heparin administration the stroke could have been the result of an embolism from thrombus forming upon the endocardial surface of the infarcted myocardium.

But the gradual disturbance of the patient's haematological picture suggests that this relatively late complication might also have been the result of a thrombotic process. There is some doubt as to the effects of viper venom. Bhargava *et al.*[3] proposed that deficiency of multiple coagulation factors as well as the extent of such a deficiency is highly presumptive of disseminated intravascular coagulation in cases of snakebite by the viper *Echis carinatus*. According to Sarangi *et al.*,[4] however, haemorrhagic manifestations in viper bite cannot be solely a result of consumptive coagulopathy, but could be attributed to toxic vasculitis caused by a non-enzymatic fraction of the viper venom that produces endothelial damage.

On the whole, the time sequence of the clinical and laboratory findings in this case are strongly suggestive of an immediate toxic effect of the venom upon the patient's heart and of a subsequent damage to the brain by disseminated intravascular coagulation of its vascular bed. A final possibility is that the brain damage was the result of haemorrhage. The laboratory findings would not suggest that heparin was in any way responsible, but the necropsy findings by the authors previously quoted[5] indicate that the possibility of intra- or extracerebral haemorrhage directly resulting from constituents of the venom cannot be discounted.

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Br Heart J 1982; 47: 504–6

Differential response to carotid sinus pressure during sinus rhythm and atrial fibrillation

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SUMMARY In a patient who presented with syncope and palpitation left carotid sinus massage resulted in prolonged ventricular asystole during atrial fibrillation. In the same patient left carotid sinus stimulation during sinus rhythm produced no change in sinus rate and only slight PR interval prolongation. This very different response may be the result of factors which are relevant only during atrial fibrillation such as an increase in the atrial depolarisation frequency and a prolongation of the duration of the atrioventricular nodal concealment zone secondary to increased vagal activity. An increase in atrioventricular nodal refractoriness could not explain this differential response.

The cardio-inhibitory form of the hypersensitive carotid sinus reflex is a relatively common and important cause of presyncope in elderly men.[1-3] Unilateral carotid sinus massage has a variable effect on both sinus node automaticity and atrioventricular nodal conductivity.[4] Right carotid sinus stimulation, however, appears preferentially to produce sinus node slowing whereas left carotid sinus pressure is more likely to result in atrioventricular nodal conduction delay or block.[5]

We present, in this report, a patient with a history of syncope and paroxysmal atrial fibrillation who during normal sinus rhythm showed little response to right or left carotid sinus massage. Left carotid sinus pressure, however, during atrial fibrillation produced profound bradycardia and presyncope.

Case report

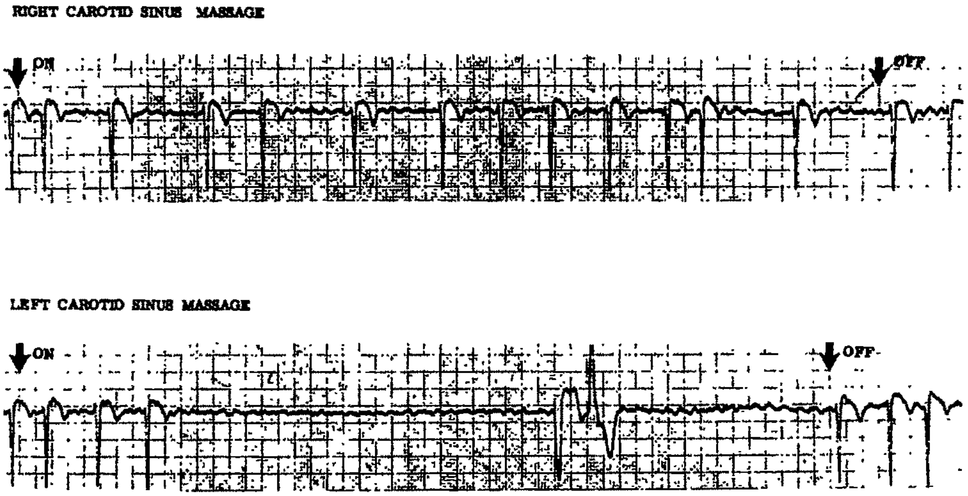
In April 1980, a 70-year-old man was referred for investigation of palpitation accompanied by presyncope and syncope. These symptoms had been occurring intermittently over the preceding 10 weeks. The patient had observed that during episodes of palpitations, presyncope could be precipitated by head turning. Twenty-four hour ambulatory electrocardiographic monitoring before admission showed sinus rhythm with intermittent sinus bradycardia, occasional Wenckebach atrioventricular block, and one episode of atrial flutter lasting four minutes.

In May 1980, the patient again presented complaining of a presyncopal episode and palpitation. At this time a 12 lead electrocardiogram showed atrial fibrillation with a variable ventricular response (75 to 145 beats per min). Physical examination disclosed normal cardiovascular findings apart from intermittent atrial fibrillation. No carotid bruits were heard. Chest radiography showed a normal cardiothoracic ratio, cardiac silhouette, and pulmonary vascularity. Routine haematology and biochemistry were also within normal limits.

While in atrial fibrillation and with continuous electrocardiographic monitoring carotid sinus stimulation was performed (Fig. 1). During right carotid sinus massage for 10 seconds a transient slowing of the ventricular rate occurred, the longest RR interval being 1·2 s. Left carotid sinus stimulation for 10 s resulted in a period of 5 s of ventricular asystole followed by two ventricular complexes and then a further 3 s of asystole. This response was accompanied by dizziness identical to the patient's spontaneous symptoms.

Four hours after admission spontaneous reversion to sinus rhythm occurred. The 12 lead electrocardiogram showed a sinus rate of 68 beats/min. The P wave showed left atrial abnormality and the PR interval was slightly prolonged at 0·22 s. The QRS complex and QT interval were normal. Carotid sinus massage was again performed with continuous electrocardiographic monitoring. There was no alteration in heart rate or rhythm. Left carotid sinus massage resulted in transient PR interval prolongation to 0·26 s (Fig. 2).

Before insertion of a permanent endocardial pacing system simple electrophysiological investigations were undertaken using a single bipolar pacing catheter positioned in the high right atrium. Continuous stan-



RIGHT CAROTID SINUS MASSAGE

LEFT CAROTID SINUS MASSAGE

Fig. 1 *Differential response to right and left carotid sinus massage during atrial fibrillation.*

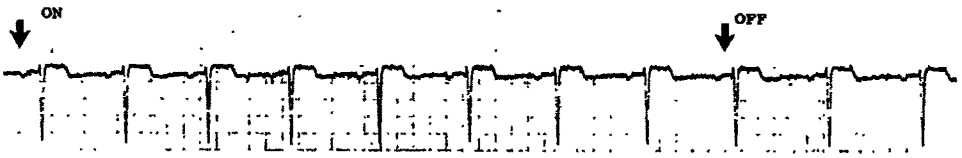


Fig. 2 *Effect of left carotid sinus massage after reversion to sinus rhythm.*

dard lead II electrocardiographic recordings were made at a paper speed of 50 mm/s before and after the administration of 3 mg atropine sulphate intravenously.

The resting PR interval was prolonged at 0·24 s. Abnormal resting values for both the raw and corrected sinus node recovery times were found (1560 ms and 620 ms, respectively). The atrioventricular Wenckebach cycle was also prolonged at 500 ms. All electrophysiological abnormalities were corrected after atropine. No direct measurements of AH or HV intervals were made and it was not possible to initiate atrial arrhythmias during the study. During sinus rhythm, and before giving atropine, however, a variety of vagotonic manoeuvres was performed (carotid sinus stimulation, eyeball pressure, Valsalva manoeuvre). No change in sinus node automaticity occurred in response to vagal stimulation. There was PR interval prolongation of up to 0·26 s during left carotid sinus massage, which did not occur after atropine.

During the six months after implantation of a ventricular demand pacemaker the patient has remained completely asymptomatic.

Discussion

The dramatic response to carotid sinus massage observed in our patient during atrial fibrillation which could not be reproduced during sinus rhythm may be explained by several factors which influence atrioventricular conduction during atrial fibrillation but not during sinus rhythm.

Vagal stimulation reduces atrial refractoriness and leads to an increase in atrial fibrillation frequency.[6-8] Both Moe and Abildskov[6] and Langendorf *et al.*[8] showed an inverse relation between the rate of atrial depolarisation at rapid frequencies and the ensuing ventricular response as a result of incomplete penetration of, or concealed conduction within, the atrioventricular node. The duration of the concealment zone within the atrioventricular node has been shown to be prolonged by increased vagal activity, further reducing the ventricular response.[6]

Vagal stimulation also increases atrioventricular nodal refractoriness and slows atrioventricular nodal conduction.[9] Since no atrioventricular block occurred during sinus rhythm in response to carotid sinus massage, an increase in atrioventricular nodal refractoriness sufficient to account for the degree of asystole seen in this patient in response to vagal stimulation during atrial fibrillation is very unlikely. Therefore, the increase in atrial input frequency and prolongation of the duration of the atrioventricular nodal concealment zone must account for most of this response.

Treatment of this cardio-inhibitory form of carotid sinus hypersensitivity by ventricular demand pacing was chosen in preference to carotid sinus denervation or anticholinergic drug treatment. Both surgical denervation and radiation treatment of the carotid sinus are unreliable,[10 11] and anticholinergic treatment, in the large doses required to abolish symptoms of carotid sinus hypersensitivity, is poorly tolerated.[12]

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Br Heart J 1982; 47: 507–10

Hypertrophic cardiomyopathy without asymmetric hypertrophy

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SUMMARY A 49-year-old woman with congestive heart failure and heart block died of cerebral embolism. Clinical and echocardiographic findings suggested a diagnosis of atypical dilated cardiomyopathy with predominantly right ventricular involvement. At necropsy, all the cardiac chambers were slightly dilated and the interventricular septum and the left ventricular wall were of normal thickness and symmetry. Histological examination, however, disclosed extensive disarray of abnormal myocardial tissue, especially in the interventricular septum. Her father had similar clinical and echocardiographic findings, while one of her brothers had typical hypertrophic cardiomyopathy at necropsy. It is likely that the patient actually had inherited hypertrophic cardiomyopathy. The case illustrates the difficulty in diagnosing hypertrophic cardiomyopathy when based solely on the left ventricular gross anatomy.

It has been generally believed that the characteristic gross anatomical features of the left ventricle in hypertrophic cardiomyopathy are preserved until death, though clinical manifestations terminally may masquerade as dilated cardiomyopathy.[1] The case we report had findings suggestive of dilated cardiomyopathy on gross anatomy, while histological findings and the findings in her family members suggested a diagnosis of hypertrophic cardiomyopathy.

Case report

A 39-year-old housewife was admitted on 9 July 1969, because of exertional dyspnoea. Cardiomegaly had been recognised since the age of 34, when she had acute renal disease. Otherwise, her past history was non-contributory. Her father and four of the eight sibs were affected by cardiomyopathy, and several family members had raised circulating heart antibody titres and type-specific streptococcal antigens. Details of this family have been published previously[2] and the present case was then case 2. Subsequent echocardiographic examinations in her father (case 1)[2] disclosed normal left ventricular dimensions, no left ventricular hypertrophy, posterior wall hypokinesis, and paradoxical septal motion (Fig. 1b). Necropsy findings in her brother (case 7)[2] have been reported as those of symmetric left ventricular hypertrophy and myocardial fibrosis.[1] Haematoxylin-eosin stained sections of the interventricular septum and the left ventricular free wall of this case were reviewed by us. We found myocardial disarray occupying extensive areas of the interventricular septum (70%) and left ventricular free wall (50%) (Fig. 2c). A few foci of small round cell infiltration were seen in the endocardium and the myocardium (Fig. 2d).

The present case was a small woman (148 cm tall, body weight 53 kg). Her heart rate was 68 beats/min, and her blood pressure 130/80 mmHg. There was evidence of cardiomegaly on physical examination. Loud third and fourth heart sounds and a grade 2/6 systolic murmur were heard at the apex. The response of the murmur to amyl nitrite inhalation did not suggest the presence of left ventricular outflow tract obstruction. Routine laboratory examinations disclosed a moderate iron deficiency anaemia, but were otherwise normal. There was a global cardiomegaly on the chest x-ray film. Electrocardiographic findings were sinus rhythm, left atrial enlargement, left ventricular hypertrophy (SV1: 0·9 mV, RV5: 2·8 mV), and slight ST depression in leads I, II, III, aVF, and V3–V6. There were no abnormal Q waves. Circulating anti-heart antibody was positive at a titre of 1 in 160 and type 18-specific anti-beta-haemolytic streptococcal antibody was positive at 1 in 3072. Dyspnoea diminished with correction of anaemia, but the x-ray film and electrocardiogram were unchanged. She was discharged on 9 August with the diagnosis of non-

This work was supported by a grant from the Japanese Ministry of Health and Welfare for the study of cardiomyopathy.

obstructive cardiomyopathy and iron deficiency anaemia.

On 17 January 1972, atrial fibrillation developed and persisted thereafter. Her subsequent course was that of progressive congestive heart failure with cardiomegaly, despite digitalis and diuretics. An echocardiogram was taken in June 1976. The left ventricular dimensions were 54 mm at end-diastole and 48 mm at end-systole. Both the interventricular septum and left ventricular free wall were 12 mm thick. All the other cardiac chambers were moderately dilated and there was a moderate pericardial effusion. A pansystolic murmur with Rivero-Carvallo's sign was heard along the left sternal border. The patient was considered to have a dilated cardiomyopathy with predominant right ventricular involvement and functional tricuspid regurgitation. Circulating antiheart antibody was present at a titre of 1 in 40 which was the last positive value obtained.

A permanent pacemaker was implanted on 25 January 1978, because of complete heart block, which subsequently altered to persistent atrial flutter with variable atrioventricular block. She was now confined to bed because of her low output state.

Bilateral leg thrombophlebitis developed in August 1978. A lung scan disclosed a few small perfusion defects, but there was no infarction shadow on the chest x-ray film. Follow-up echocardiograms showed a decrease in left ventricular dimensions to normal values, but otherwise there was no change compared with the 1976 findings (Fig. 1a). She died of cerebral embolism on 6 October 1979.

At necropsy, heart weight was 330 g. The left ventricle was slightly dilated, the major and the minor axes of the cavity being 7 and 4·5 cm, respectively, and the thickness of the wall being 10 to 12 mm. There was no asymmetry of the left ventricular wall, as shown in Fig. 2a. The other cardiac chambers were dilated, and there were jet lesions in the atria suggesting atrioventricular valve regurgitation. The valves were normal. A screw electrode was fixed on the right ventricular wall, around which there was fibrotic adhesion of the pericardium. Otherwise, there was no evidence of pericarditis. The aorta and the coronary arteries were normal. The lungs were also normal. In the brain, a large infarct in and around the internal capsule and a few haemorrhagic foci in the pons were seen. Old and fresh infarcts were seen in the right kidney and the spleen. The source of the systemic emboli was obscure, since there was no thrombus in the cardiac chambers or the pulmonary veins. Systemic veins were examined to the level of the femoral and subclavian, and no thrombus found. The liver showed evidence of cardiac cirrhosis.

On histology, myocardial disarray was seen throughout the left ventricular wall, and was extensive particularly in the interventricular septum, occupying about 70% of the equatorial transsectional area (Fig. 2b). Disarray was prominent also in the anterolateral left ventricular wall and the anterior right ventricular wall. Many whorls were seen. Interstitial fibrosis was also prominent. Myocardial fibres in the disorganised tissue were branched in peculiar forms and were variable in size. Many fibres were thick, some being 90 μm, but were short and interrupted by fibrous tissue. There were areas of myocytolysis, leaving only the sarcolemmal sheath. Nuclei were frequently hypertrophied and of bizarre shape. Nuclear halo was present, but was not extensive. The intramyocardial small coronary arteries

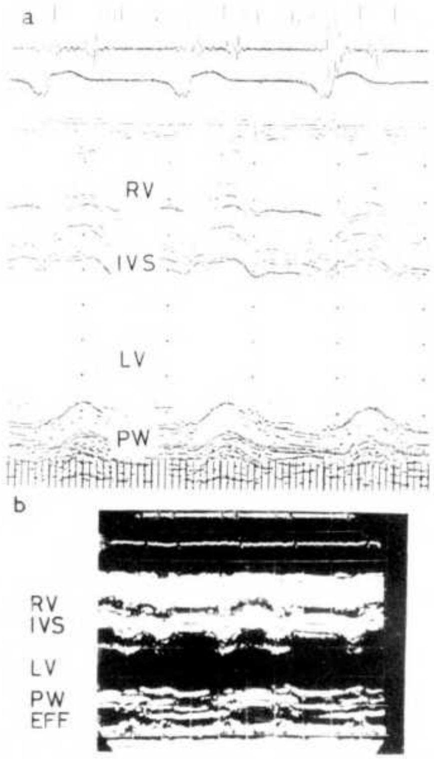

Fig. 1 *Echocardiograms of the present case (a) and her father (b). In (a), which was taken in March 1978, both the interventricular septum (IVS) and the left ventricular posterior wall (PW) measured 6 to 7 mm. End-diastolic dimension of the right ventricle (RV) was 30 mm, while that of the left ventricle (LV) was 45 mm. Motion of the interventricular septum was paradoxical. An echocardiogram of her father (b) was essentially similar to (a), showing normal thickness of the interventricular septum (10 mm) and posterior wall (10 mm), normal left ventricular dimension (45 mm), and paradoxical interventricular septal motion. Posterior wall motion was hypokinetic and there was pericardical effusion (EFF).*

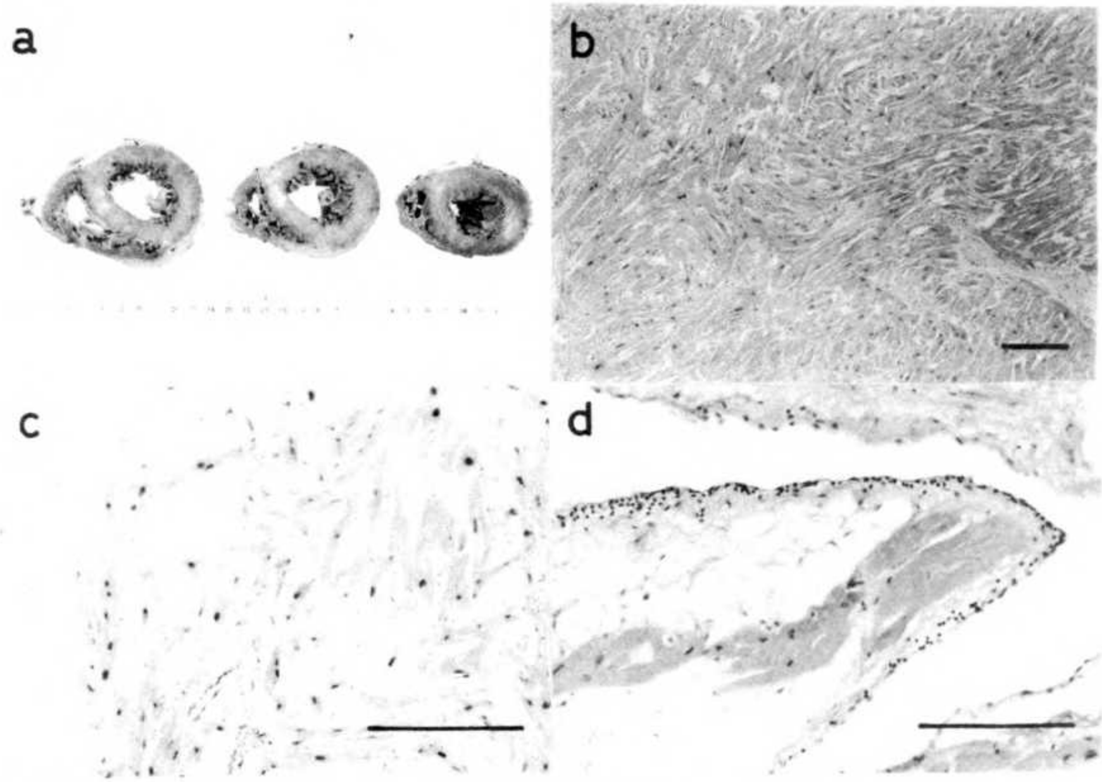

Fig. 2 *Necropsy findings in the present case (a, b) and in her brother (c, d). In (a), sequential cross-sections of the heart after fixation are shown. There is no asymmetric septal hypertrophy. The interventricular septum, however, contains large amounts of disarrayed myocardial fibres as in (b) (haematoxylin-eosin stain). Many myocardial fibres are hypertrophied and nuclei are bizarre in shape. Prominent myocardial disarray is also seen in her brother's interventricular septum (c) (haematoxylin-eosin stain). A few foci of small round cell infiltration are seen in the endocardium (d) (haematoxylin-eosin stain) and the myocardium in the latter, but not in the present case. The bars in the figure show 500 μm in (b) and (c), and 200 μm in (d).*

were occasionally narrowed with medial hypertrophy. There was no inflammatory cell infiltration.

Discussion

Myocardial disarray in the interventricular septum, when extensive as in our patient, has been considered a specific finding of hypertrophic cardiomyopathy.[3 4] Extreme thickness of myocardial fibres, extensive fibrosis, bizarre muscle nuclei, disappearing myocardial fibres with nuclear halos, whorls, and short runs of fibres, in combination, are highly suggestive of the diagnosis of hypertrophic cardiomyopathy.[5 6] The findings of hypertrophic cardiomyopathy in her brother at necropsy, and the overall family history suggesting autosomal dominant inheritance of the cardiomyopathy were also consistent with this diagnosis.[7 8]

On the other hand, asymmetric hypertrophy was not seen on echocardiograms, and the necropsy findings were those (macroscopically) of dilated cardiomyopathy. The clinical diagnosis of hypertrophic cardiomyopathy is based on the recognition of undue left ventricular hypertrophy, particularly in the form of asymmetric septal hypertrophy.[9 10] Asymmetric septal hypertrophy has been seen even terminally in hypertrophic cardiomyopathy with clinical manifestations masquerading as dilated cardiomyopathy,[1] and even after the development of left ventricular dilatation.[11] Asymmetric hypertrophy, however, is not strictly a *sine qua non* for the diagnosis of hypertrophic cardiomyopathy, since there are occasional cases with left ventricular hypertrophy which are symmetrical.[12] If terminal ventricular dilatation occurs in such hearts, the gross anatomical findings may mimic those of dilated cardiomyopathy. Olsen[5] has described five cases resembling dilated cardiomyopathy, but indistinguishable from hypertrophic cardiomyopathy histologically. None of the five had a definite family history of hypertrophic cardiomyopathy. In the present case, the existence of necropsy-proven hypertrophic cardiomyopathy in the family members suggests that the patient's cardiomyopathy is within the spectrum of this disease.

The relation between the immunological and cardiological abnormalities is obscure. According to Das *et al.*,[13] antiheart antibody is frequently positive in hypertrophic cardiomyopathy, and the titre is high especially in the stage of progression. In the present case, however, antiheart antibody was positive only in the early stages and did not correlate with the clinical course. Immunological studies were not carried out in her brother, though the focal cell infiltration in his heart may suggest a possible link between the immunological abnormalities and the cardiomyopathy in the family.

We thank Dr Akihiro Takatsu, Department of Forensic Medicine, University of Tokyo, for his cooperation on the family study.

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Correspondence

Br Heart J 1982; **47**: 511

Failure of nifedipine treatment in primary pulmonary hypertension

Sir,

In an attempt to emulate the success described by Camerini *et al.* in a recent article in the British Heart Journal,[1] we tried nifedipine in the treatment of a 36-year-old woman who had both clinical and haemodynamic findings of primary pulmonary hypertension.

The patient was studied using a Swan-Ganz catheter; the procedure used by Camerini *et al.* was not changed. The following results were obtained:

Only diazoxide at the lowest dose appeared to decrease total pulmonary resistance significantly. Nifedipine failed to do so. Other trials with molsidomine (a new long acting vasodilator) and hydralazine were also unfruitful.

As proposed by Klinke,[2] drugs used to attempt to treat primary pulmonary hypertension need acute testing before being started on a long term basis; moreover, monitoring of the pulmonary vascular pressure is mandatory to avoid aggravating the condition. We would like to emphasise that whereas primary pulmonary hypertension may occasionally be ameliorated by various drugs, this response is individual and not the rule.

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Note: This is a further letter to correspondence published in *Br Heart J* 1981; **46**: 230–1. Dr Camerini was shown this letter but thought that his earlier letter covered the points now raised in this one by Berkenboom *et al.*

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1 Camerini F, Alberti E, Klugmann S, Salvi A. Primary pulmonary hypertension: effects of nifedipine. *Br Heart J* 1980; **44**: 352–6.
2 Klinke WP. Treatment for primary pulmonary hypertension. *Am Heart J* 1980; **100**: 587–8.

1. *Nifedipine* (20 mg sublingually)

	HR *(beats/min)*	*CO* *(l/min)*	$\bar{P}A$ *(mmHg)*	*TPR* *(dyne s cm^{-5})*	$\bar{P}a$ *(mmHg)*	*TSR* *(dyne s cm^{-5})*
Basal	98	4·3	50	929	92	1709
30′	102	4·8	59	982	91	1697
60′	104	4·8	59	982	87	1614

2. *Diazoxide* (in pulmonary artery)

	HR *(beats/min)*	*CO* *(l/min)*	$\bar{P}A$ *(mmHg)*	*TPR* *(dyne s cm^{-5})*	$\bar{P}a$ *(mmHg)*	*TSR* *(dyne s cm^{-5})*
Basal	115	3·5	62	1415	85	1940
50 mg	125	4·05	55	1085	90	1775
100 mg	132	4·35	62	1138	87	1598
100 mg	137	4·35	61	1120	82	1506

HR; heart rate; CO, cardiac output; $\bar{P}A$, mean pulmonary arterial pressure; $\bar{P}a$, mean systemic arterial pressure; TSR, total systemic resistance; TPR, total pulmonary resistance.

Notices

Br Heart J 1982; 47: 512

Subacute bacterial endocarditis

A survey is currently being carried out by the British Cardiac Society and the Medical Services Study Group of the Royal College of Physicians. Though improvement of dental prophylaxis is one objective, the survey is already yielding other valuable information. It is hoped that proformas will be received in respect of a high proportion of patients with subacute bacterial endocarditis in the British Isles seen during 1981 and 1982 and readers are asked to arrange for them to be submitted in respect of any cases that come to their notice. Proformas can be obtained from Sir Cyril Clarke, Medical Services Study Group, King's Fund Centre, 126 Albert Street, London NW1 7NF (tel. 01-267 6111, ext. 263) to whom they should be returned.

Erratum

Aortic regurgitation: detection of left ventricular dysfunction by exercise echocardiography (1981; 46: 380–8). On page 383, Fig. 4 should have displayed the p values as follows:

$p<0.001$ for normal, $p<0.001$ for group 1, NS for group 2, and $p<0.05$ for group 3. We regret the error.

Future meetings

(1) Cardiovascular System Dynamics Society Vth International Conference, Oxford, 28 September to 1 October 1982. For further details write to Dr G d J Lee, Cardiac Department, John Radcliffe Hospital, Oxford.

(2) International Symposium on Coronary Arteries in Infants and Children, Tel Aviv, Israel, 17 to 22 October 1982. For further details write to D A Schneeweiss, Secretariat: PO Box 29784, Tel Aviv 61297, Israel.

(3) VIIth World Symposium on Cardiac Pacing, 1 to 5 May 1983, Vienna, Austria. For information write to A 1107, PO Box 80, Vienna, Austria.

(4) The Autumn Meeting of the British Cardiac Society will take place at Wembley on 6 and 7 December 1982 and the closing date for receipt of abstracts is 11 August 1982.

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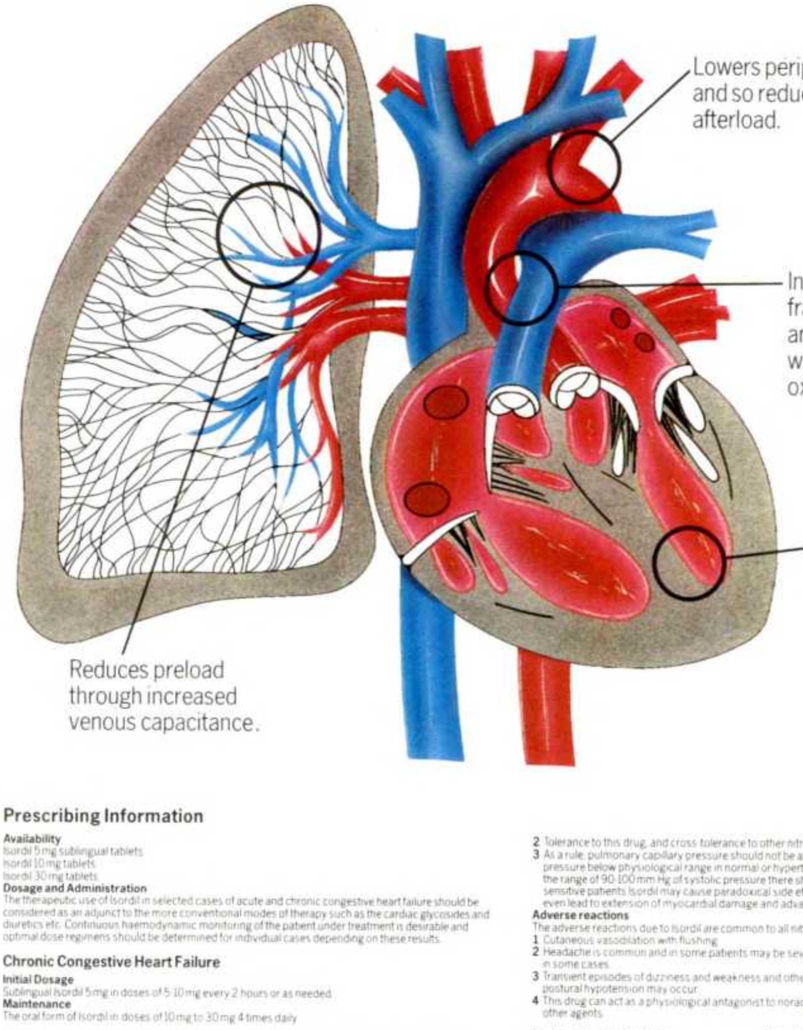

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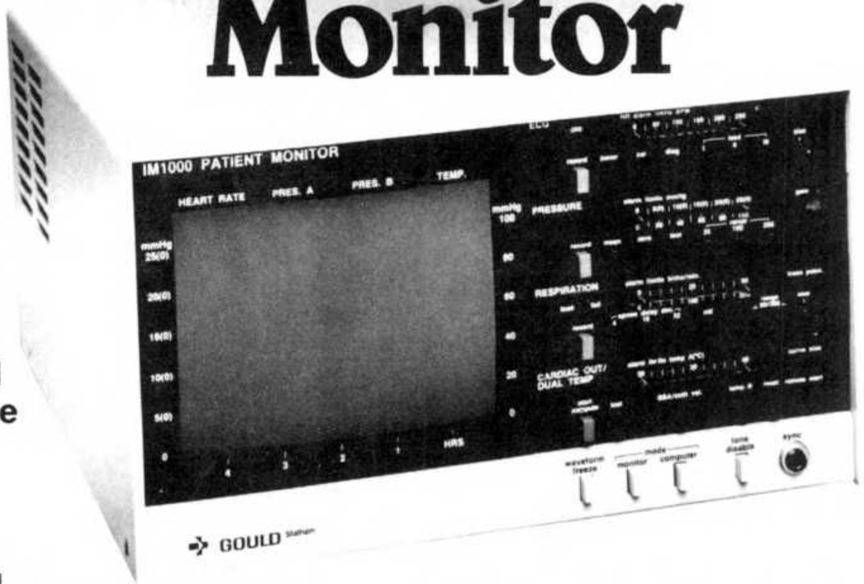

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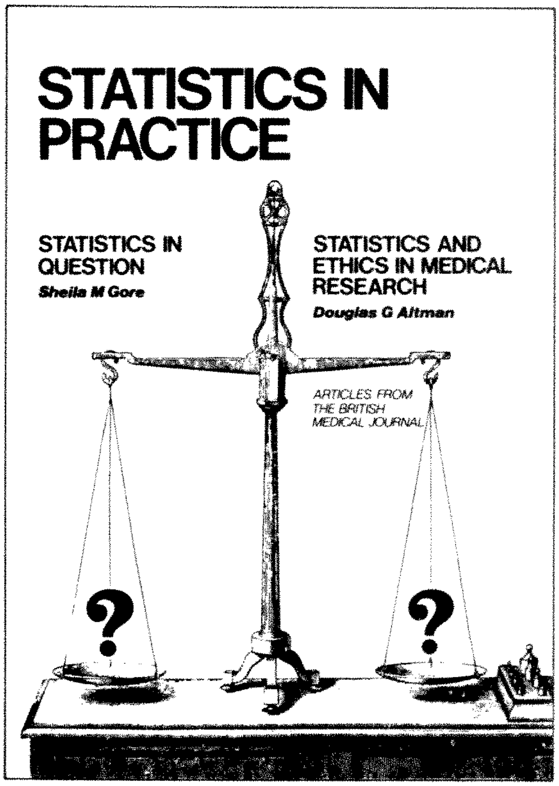

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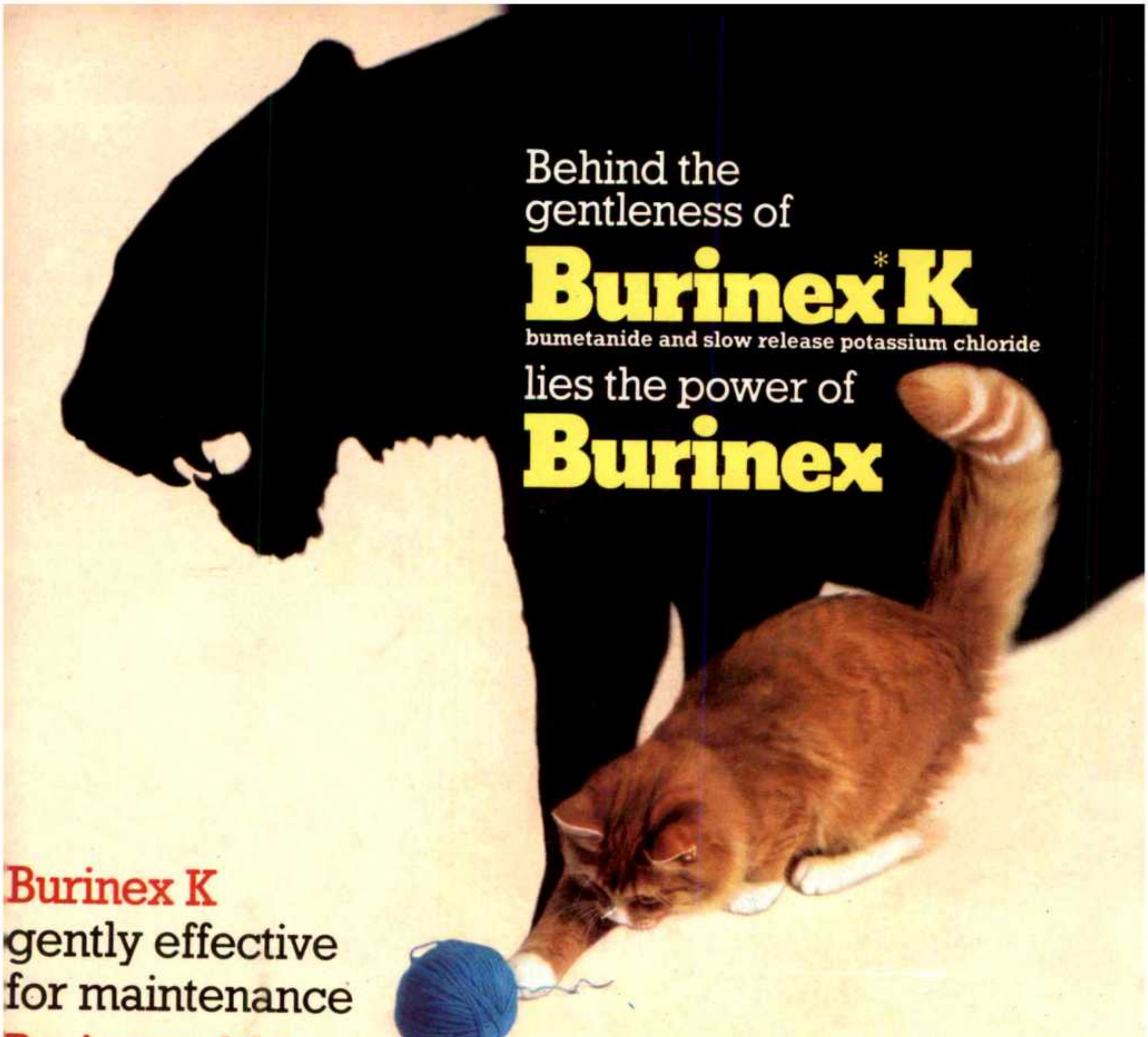

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(1) *Standard journal article*—(List all authors when six or less; when seven or more, list only first three and add *et al.*):
Walmsley R. Anatomy of left ventricular outflow tract. *Br Heart J* 1979; **41**: 263–7.

(2) *Books and other monographs:*
Macartney FJ, Partridge JB, Shinebourne EA, Tynan MJ, Anderson RH. Identification of atrial situs. In: Anderson RH, Shinebourne EA, eds. *Paediatric cardiology 1977*. Edinburgh, London: Churchill Livingstone, 1978: 16-26.

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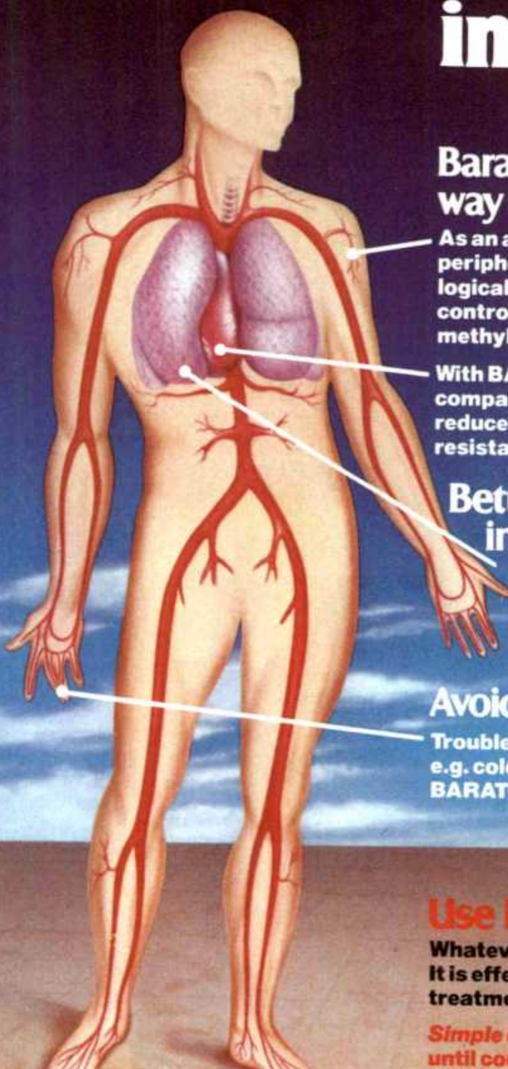
Why Baratol is a better choice than beta-blockers in hypertension



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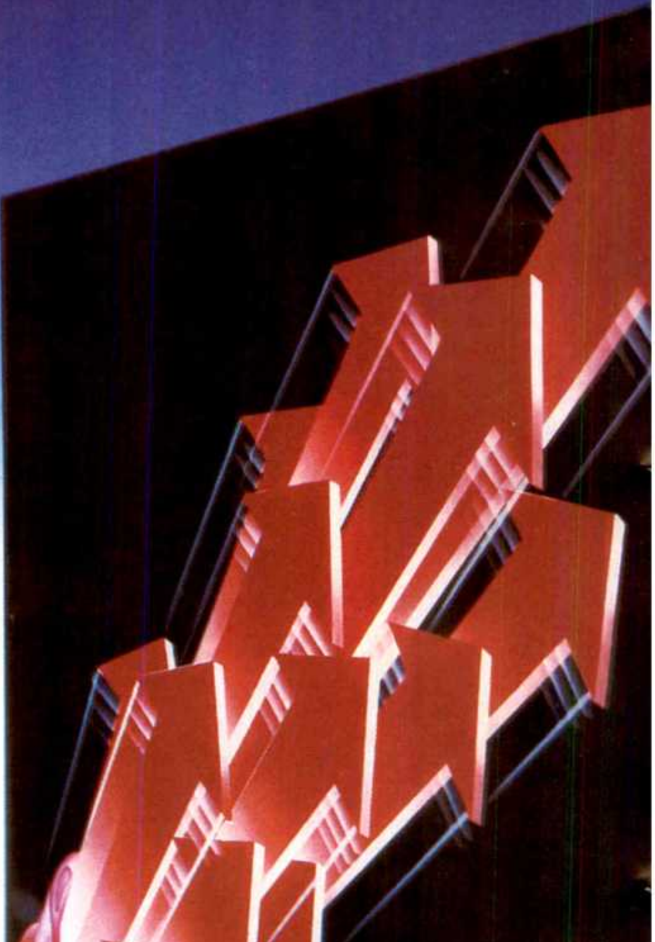

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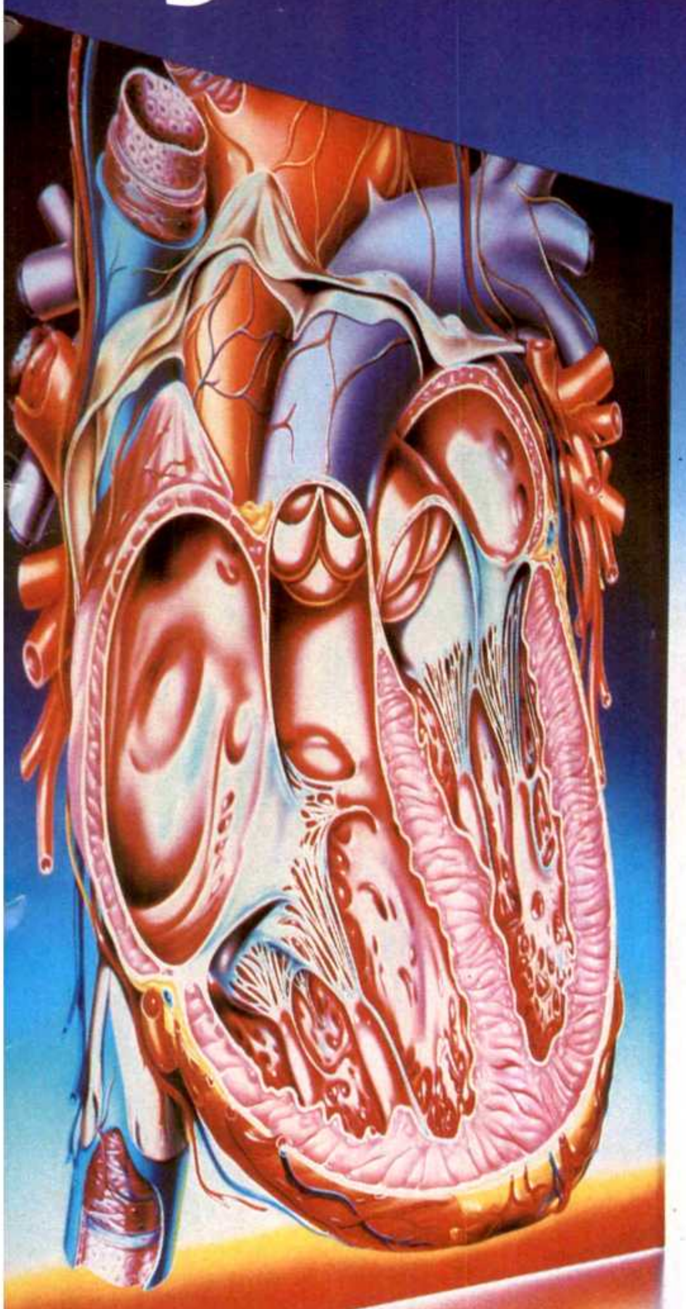

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Side Effects Dizziness, drowsiness and lack of energy are the most common.

1. Turner, A.S., et al. Med. J. Aust., Spec., Suppl., (1977), **2**, 33-37.
2. Fauchald, P., et al. Excerpta Medica International Symposium, Vienna, November (1978), 85-93.
3. Bossi, M, et al. Excerpta Medica Symposium, Tokyo (1978), 107.
4. Hutton, I, et al. European Prazosin Symposium (1978), 138.

Dosage

Congestive Heart Failure Suggested Initial Daily Dose Range: 0.5mg increasing to 1.0mg t.i.d., or q.i.d. Usual Daily Maintenance Dose: 4.0mg to 20mg in divided doses.

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Why is Finland no longer the world's black spot for heart attacks?

The prevalence of CHD has been greater in Finland than in any other country – with the highest rates in the county of North Karelia.

Because of this, the North Karelia Project was initiated – a comprehensive five-year experiment attempting to control cardiovascular diseases with a community programme.

By the end of the project, the levels of the 3 main risk factors for CHD among North Karelians were markedly reduced.

Overall, the mean net reduction in the estimated CHD risk was significant – 17.4% among men, 11.5% among women.*

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Editorial

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QT and action potential duration

E M VAUGHAN WILLIAMS

From University Department of Pharmacology, Oxford

Depolarisation of cardiac muscle is achieved by "fast inward current", carried by sodium ions, through channels which are inactivated within about one millisecond. When the cells are repolarised (by a net efflux of potassium ions) the process of inactivation of fast channels is rapidly reversed. The class 1 antiarrhythmic drugs delay the disappearance of inactivation until long after repolarisation is complete, and so reduce the probability of re-excitation at short intervals, thus suppressing premature extrasystoles and tachycardia. In theory, it should be possible to produce a similar extension of refractory period by delaying the repolarisation itself, and a drug with this property was sought for many years. Quinidine and disopyramide[1] caused minor delays of repolarisation, but both were primarily class 1 agents, and in addition had undesirable anticholinergic activity.

Eventually it was found that amiodarone, already in use for many years as an antianginal drug, prolonged action potential duration, and on theoretical grounds seemed worthy of trial as an antiarrhythmic agent. It was indeed shown to have an antiarrhythmic action in rabbits[2] and dogs,[3] but two important questions remained. Would the prolongation of action potential duration occur in man, and, if so, would this property be antiarrhythmic?

There was an understandable reluctance to accept that a drug which prolonged action potential duration could prevent or abolish cardiac arrhythmias. At the same meeting in Elsinore at which I proposed a classification of antiarrhythmic actions, which included the prolongation of action potential duration as "class 3", Ward[4] described the familial propensity to ventricular arrhythmias, precipitated by exercise or emotion, in association with a long QT interval, not unlike cases previously noted by Romano *et al.*[5] and by Ward himself.[6] The phenomenon of "R on T" has long been regarded as a harbinger of impending life-threatening arrhythmia, and a long QT has been proposed as a predictor of sudden death.[7]

It must be emphasised that QT is not a measure of action potential duration. Though a uniform prolongation of ventricular action potential duration can be detected as a lengthened QT interval, QT itself represents the time from the first depolarisation to the final repolarisation in the axis of the selected leads. It records the algebraic sum of millions of individual action potential durations and could conceal within itself a number of *short* action potential durations juxtaposed to long ones. The first successful use of amiodarone as an antiarrhythmic agent in man was reported in 1972 by Ferrero and Benabderhamane in atrial flutter.[8] Amiodarone was later shown to prolong action potential duration, monophasically recorded with suction electrodes.[9]

Long term treatment of rabbits with beta blockers induces several adaptive changes in the myocardium, which persist long after the drugs have been eliminated from the body.[10] This "adaptation syndrome" included a prolongation of action potential duration and QT, and both these effects have been shown to occur in man.[11-13] These observations could explain both the prevalence of arrhythmias in the long QT syndrome and the success of antisympathetic therapy by left stellate ganglionectomy or beta blockade. The long QT syndrome is said to be associated with a preponderance of sympathetic innervation from the left stellate ganglion, and a deficit on the right, accounting for a reduced tachycardia of exercise in patients, since the normal sinoatrial node is primarily innervated from the right side. The ventricular fibres deprived of their (right) sympathetic innervation, would adapt by having very long action potential durations (hence the long QT). During exercise or emotion the myocardial regions supplied by the left stellate would receive excessive sympathetic drive, since they would have to compensate for the failure of the non-innervated areas to increase their activity. The myocardium would thus be subjected to two highly arrhythmogenic influences, the juxtaposition of shortened action potential duration in the innervated fibres next to adapted and unresponding long action potential duration in the remainder, and the probability of the awakening of subsidiary pacemaking cells by the aggravated adrenergic stimulation. Abolition of the excessive sympathetic drive by surgery or by adrenergic blockade would reduce the heterogeneity of action potential duration and though peak performance might be diminished this would be a reasonable price to pay for a lessened risk of sudden death.

In hypertrophic cardiomyopathy there is also evidence of augmented adrenergic innervation, and it is of interest that amiodarone has recently been reported to be of benefit in arrhythmias occurring in hypertrophic cardiomyopathy.[14] It would be rational, therefore, to investigate whether amiodarone could reduce the incidence of arrhythmias in the long QT syndrome.

In spite of the above evidence, it is still unproven that a prolongation of action potential duration, uniform and homogeneous though it may be, can truly be regarded as responsible for an antiarrhythmic effect. Amiodarone has an acute antisympathetic action, of a non-competitive type,[15] and it restricts transmitter release[16]; both these properties could exert an acute (class 2) antiarrhythmic effect. Similarly, the protection afforded by prolonged beta blockade against reinfarction and sudden death could be attributed to an oxygen sparing effect or even to an increased myocardial capillarity,[17] rather than to a class 3 antiarrhythmic action. The drug sotalol could provide a useful tool for testing whether prolongation of action potential duration does contribute some antiarrhythmic efficacy, because it not only prolongs action potential duration at clinical concentrations, but is devoid of class 1 direct membrane action, which might otherwise be a complicating factor. Two papers in the current issue of this journal suggest that sotalol has a more potent antiarrhythmic action than could be attributed to beta blockade alone. Another compound recently shown to prolong action potential duration in cardiac muscle is melperone,[18] already in use as a tranquilliser.

Amiodarone has no direct negative inotropic action and, provided that it is given orally to reduce the hypotension which can occur on acute administration intravenously, there seems to be no reason why it should not be tested in combination with beta blockers for the treatment of life threatening arrhythmias occurring in hypertrophic obstructive cardiomyopathy, long QT syndrome, or pre-excitation syndromes. With several drugs now available which prolong action potential duration in atrial and ventricular muscle in a reasonably homogeneous manner, class 3 antiarrhythmic action may, perhaps, progress from unproven theory to practical reality.

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Electrophysiological effects of sotalol—just another beta blocker?

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SUMMARY The electrophysiological effects of intravenous sotalol hydrochloride (0·4 mg/kg) were assessed in 24 patients, including 13 with the Wolff-Parkinson-White syndrome, undergoing routine electrophysiological study. Fifteen to 30 minutes after sotalol administration there was a significant increase in sinus cycle length and in sinus node recovery time. There was a small increase in the AH interval, but the HV interval was unchanged. The QT and JT intervals, measured during sinus rhythm, were both increased. The atrial, ventricular, and atrioventricular nodal effective refractory periods were all prolonged, as was the atrioventricular nodal functional refractory period. In 13 patients with ventricular pre-excitation there was an increase of the accessory pathway anterograde and retrograde effective refractory periods. In 12 of these 13 sotalol was given during atrioventricular re-entrant tachycardia, resulting in termination in five. Tachycardia cycle length increased in all patients, with the major effect being in the atrioventricular direction. Though some of the effects seen in these patients are consistent with the beta adrenergic antagonist properties of sotalol, the effect on atrial, ventricular, and accessory pathway effective refractory periods and on ventricular repolarisation is not typical of that observed with other beta blockers but may be the result of lengthening of the action potential duration. These findings suggest that sotalol may be a more versatile antiarrhythmic agent than other beta receptor antagonists.

Sotalol hydrochloride was initially described as a pure beta adrenergic antagonist with class II antiarrhythmic action, but lacking cardioselectivity, intrinsic sympathomimetic effect, or local anaesthetic properties.[1-3] Subsequent animal investigations have shown that sotalol also causes a large increase in the action potential duration, similar to that seen with amiodarone.[4 5] These observations have recently been supplemented by the findings of Edvardsson *et al.*[6] who noted prolongation of right ventricular monophasic action potentials in man. These effects are consistent with class III action.[3]

A previous pilot study from our laboratory failed to show conclusively whether or not sotalol possesses class III antiarrhythmic activity.[7] The present work was performed in order to clarify further the clinical cardiac electrophysiological effects of sotalol in a group of patients including those with the Wolff-Parkinson-White syndrome.

Patients and methods

Twenty-four consecutive patients, aged between 12 and 73 years, were investigated during routine electrophysiological study. Nineteen had complained of recurrent palpitation, three of dizzy spells, and two had suffered syncopal attacks. Thirteen patients (group A) had electrophysiological evidence of pre-excitation and were considered to have the Wolff-Parkinson-White syndrome. Atrioventricular re-entrant tachycardia had been documented in all 13. Eleven patients (group B) showed no evidence of pre-excitation and had a variety of electrophysiological diagnoses. Clinical and electrocardiographic details of all patients are shown in the Table.

Electrophysiological studies were performed as previously described.[8 9] All patients gave informed consent and were studied in the non-sedated, post-absorptive state. Cardioactive medications were stopped for at least three drug elimination half-lives before study. High right atrial and His bundle electrograms were recorded in all patients. Distal and proximal

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*Recipient of a British Heart Foundation Fellowship.

†Recipient of a grant from the Joint Research Board, St Bartholomew's Hospital.

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Table *Patient details*

Case No.	*Age (y)*	*Sex*	*Symptoms*	*Electrocardiogram*	*Electrophysiological diagnosis*
Group A					
1	23	F	Syncope	WPW B	Septal AP, AVRT
2	48	M	Palpitation	WPW A	Left-sided AP, AVRT
3	56	F	Palpitation	WPW A	Left-sided AP, AVRT
4	24	M	Palpitation	WPW A	Left-sided AP, AVRT
5	37	M	Palpitation	WPW A	Left-sided AP
6	22	F	Palpitation	WPW A	Left-sided AP, AVRT
7	51	M	Presyncope	WPW A	Left-sided AP, AVRT
8	32	M	Palpitation	WPW A	Left-sided AP, AVRT
9	13	F	Palpitation	WPW A	Left-sided AP, AVRT
10	73	M	Palpitation	WPW A	Left-sided AP, AVRT
11	12	F	Palpitation	WPW A	Left-sided AP, AVRT
12	23	F	Palpitation	WPW A	Left-sided AP, AVRT
13	50	F	Palpitation	WPW A	Left-sided AP, AVRT
Group B					
14	58	M	Palpitation	RBBB	Atrial tachycardia
15	60	F	Syncope	LBBB	Bundle branch disease
16	39	M	Palpitation	Normal	Atrial fibrillation
17	61	M	Palpitation	Normal	Dual AH, AVNRT
18	45	F	Palpitation	Normal	Dual AH, AVNRT
19	20	M	Presyncope	Long PR	Vagotonia
20	43	M	Palpitation	Short PR	Short AH
21	65	M	Presyncope	RBBB	Bundle branch disease
22	44	M	Palpitation	Short PR	Short AH
23	49	M	Palpitation	Ant. MI	Ventricular tachycardia
24	32	M	Palpitation	Normal	Normal

Ant. MI, anterior myocardial infarction; AP, accessory atrioventricular pathway; AVNRT, atrioventricular nodal re-entrant tachycardia; AVRT, atrioventricular re-entrant tachycardia; dual AH, functional duality of AH conduction; LBBB, left bundle-branch block; RBBB, right bundle-branch block; WPW, Wolff-Parkinson-White abnormality.

coronary sinus electrograms were recorded using a quadripolar electrode catheter in all group A patients and in several from group B. Stimulating electrodes were positioned in the high right atrium and right ventricular apex. Three or four surface electrocardiographic leads were recorded simultaneously. Recordings were made at a paper speed of 100 mm/s using a Mingograf ink pen recorder*, and stimulation was achieved with a Devices 4279 isolated stimulator†, emitting square wave pulses of 2 ms duration at approximately twice the diastolic threshold.

The following measurements were repeated using a similar technique 15 to 30 minutes after the infusion of sotalol (0·4 mg/kg) given over five minutes: sinus cycle length (averaged over 10 consecutive cycles); sinus node recovery time[10] after high right atrial pacing for one minute at rates of 90, 120, and 150 beats per minute; PA,[9 11] AH, and HV[9 12 13] intervals; QT interval[9 14]; QRS duration (measured from the earliest point of ventricular activation to the latest J point in any lead); atrial,[9 15] ventricular,[9 16] atrioventricular nodal,[9 15] accessory pathway anterograde and retrograde[9 17] effective refractory periods; atrioventricular nodal functional refractory period.[9 15]

The corrected QT was calculated using Bazett's correction: $QTc=QT/\sqrt{RR}$ in seconds.[18] The JT interval (QT-QRS) was calculated as a further index of ventricular repolarisation, relatively independent of changes in depolarisation.[9] To minimise further the rate-related changes in the QRS duration and in the QT and JT intervals, these variables were also measured during atrial pacing at identical rates both before and after drug administration.

Refractory periods were measured using the extrastimulus technique,[13] at a constant driven pacing cycle length of 600 ms unless this exceeded the spontaneous sinus cycle length, when a slightly shorter cycle length was used.

Tachycardia cycle length was also measured (the mean atrial to atrial interval during tachycardia averaged over 10 consecutive beats), as were the tachycardia atrioventricular (intrinsicoid deflection of the low right atrial electrogram to the onset of the ventricular activation) and ventriculoatrial (onset of ventricular activation to the intrinsicoid deflection of the low right atrial electrogram) intervals. Where tachycardia was terminated by sotalol, the tachycardia intervals after sotalol were measured from the 10 beats immediately before reversion.

Statistical analyses were performed using Student's two tailed t test for paired data, except for the measurements of accessory pathway refractoriness, where the Wilcoxon sign rank test was used in order to include patients in whom initial accessory pathway refractory period measurements were limited by the refractoriness of the paced chamber or in whom sotalol caused complete conduction block.

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*Siemens-Elema, Stockholm, Sweden.

†Digitimer Ltd., Welwyn, Hertfordshire, England.

Results

The dose of sotalol used varied from 18 to 32 (mean 24) mg. All measurements are written as the mean value ± one standard deviation from the mean.

SINUS NODE FUNCTION

Sinus cycle length increased in all patients from 739±107 to 869±109 ms ($p<0\cdot001$). Sinus node recovery time, measured only in group B patients, increased from 1084±302 to 1270±301 ms ($p<0\cdot01$).

CONDUCTION

There was a small increase in the PA interval from 43±13 to 45±13 ms ($p<0\cdot02$), and a larger increase in the AH interval from 82±28 to 94±32 ms ($p<0\cdot001$). The AH interval could not be measured in one group A patient (case 1) because of the degree of pre-excitation. In the patients without pre-excitation (group B) there was no significant change in the HV interval (44±12 to 45±13 ms). In these patients there was no significant increase in the QRS duration measured during sinus rhythm (102±20 to 106±19 ms) or during constant rate atrial pacing (104±19 to 106±20 ms). The QT interval increased from 401±45 to 427±38 ms ($p<0\cdot01$) (Fig. 1a), and the paced QT interval from 388±43 to 400±37 ms ($p<0\cdot01$) (Fig. 1b), but the QTc was not significantly increased (450±48 to 455±46 ms) (Fig. 1a). The JT interval increased from 300±44 to 321±35 ms ($p<0\cdot02$) (Fig. 1a) and the paced JT interval from 284±37 to 294±31 ms ($p<0\cdot05$) (Fig. 1b).

REFRACTORINESS

The atrial effective refractory period increased from 216±38 to 233±40 ms ($p<0\cdot01$), and effective refractory period of the ventricle from 231±30 to 242±31 ms ($p<0\cdot01$). The effective refractory period of the atrioventricular node was limited by atrial refractoriness or obscured by accessory pathway conduction in 12 patients. In the remaining 12 there was an increase from 294±87 to 338±90 ms ($p<0\cdot001$). The functional refractory period of the atrioventricular node was limited by atrial refractoriness in 11 patients and in the remaining 13 increased from 417±92 to 467±86 ms ($p<0\cdot001$). The effective refractory period of accessory pathway in the anterograde direction was limited by atrial refractoriness in three patients, increased in eight, decreased in one, and remained unchanged in the other, an overall increase from 317±88 to 350±81 ms ($p<0\cdot02$). The effective refractory period of the accessory pathway in the retrograde direction was limited by ventricular refractoriness in three patients. In the other 10 patients, complete accessory pathway block occurred in two (effective refractory period of the accessory pathway in the retrograde direction >600 ms), refractoriness increased in six and decreased in two, an overall change from 296±40 to 371±139 ms ($p<0\cdot05$).

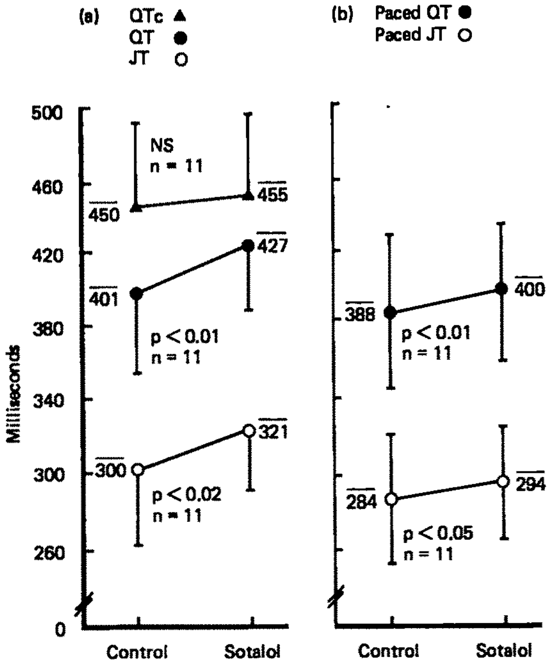

Fig. 1 *The effect of sotalol on indices of ventricular repolarisation. The QT, QTc, and JT intervals are shown in panel (a); the QT and JT intervals during constant rate atrial pacing are shown in panel (b).*

TACHYCARDIA INTERVALS

Sotalol was given during tachycardia in 12 out of the 13 group A patients, terminating it in five. An example of anterograde termination is shown (Fig. 2). The mean total cycle length increased from 355±64 to 413±54 ms ($p<0\cdot001$) (Fig. 3a). This increase occurred predominantly in the atrioventricular direction, the tachycardia atrioventricular interval increasing from 230±69 to 286±54 ms ($p<0\cdot001$), with only a small increase in the tachycardia ventriculoatrial interval from 125±25 to 132±25 ms ($p<0\cdot01$) (Fig. 3b).

Discussion

In 1965 Lish *et al.*[1] showed that sotalol, in common with other beta antagonists, prevented isoprenaline-induced tachycardia. Since then numerous reports have shown that sotalol is moderately effective for the

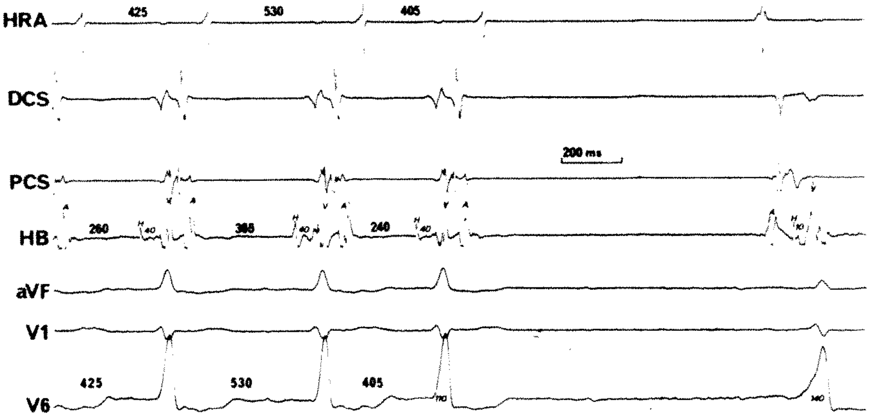

Fig. 2 *Electrographic recording of anterograde termination of an atrioventricular re-entrant tachycardia by sotalol in a patient with the Wolff-Parkinson-White syndrome. Note the alternation of cycle length before reversion occurs. High right atrial (HRA), distal coronary sinus (DCS), proximal coronary sinus (PCS), and His bundle (HB) electrograms are shown, together with three standard surface leads (aVF, V1, V6). V=ventricular electrogram, A=atrial electrogram. The paper speed is 100 mm/s.*

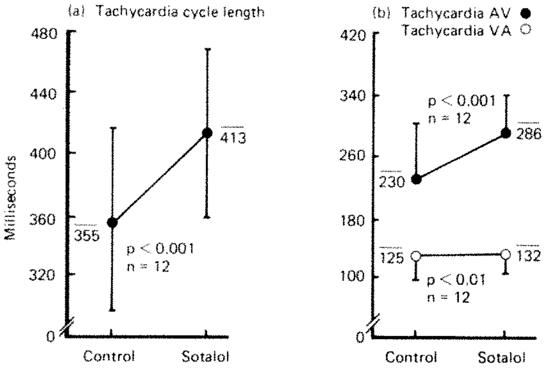

Fig. 3 *The effect of sotalol on tachycardia cycle length and on the tachycardia atrioventricular (AV) and ventriculoatrial (VA) intervals.*

treatment and prevention of a wide spectrum of arrhythmias.[19-21] Several beta receptor antagonists have been investigated during cardiac electrophysiological study[22-24] and, like sotalol, most prolong sinus cycle length and the sinus node recovery time[25] as well as increasing atrioventricular nodal conduction time (AH interval) and atrioventricular nodal refractoriness. Sotalol, in common with pindolol[26] and atenolol,[27] has also been shown to increase atrial refractoriness.

Although the antiarrhythmic properties of sotalol have previously been ascribed to beta receptor antagonism alone,[28 29] Singh and Vaughan Williams[4] reported that sotalol caused prolongation of atrial and ventricular action potentials in isolated rabbit and cat myocardium. It also increased the QTc interval in anaesthetised guinea-pigs, but had negligible local anaesthetic (membrane stabilising) effects. From these studies it was concluded that sotalol has class III antiarrhythmic activity in addition to beta receptor antagonism.

Ward *et al.*[7] have previously reported a limited clinical study showing that sotalol (0·4 mg/kg) causes a significant increase in sinus cycle length, sinus node recovery time, the AH interval, the atrial effective refractory period, and the effective and functional refractory periods of the atrioventricular node, but a statistically insignificant increase in the effective refractory period of the ventricle. None of the patients studied had an atrioventricular accessory pathway, and indices of repolarisation such as the QT and JT intervals were not examined. Edvardsson *et al.*[6] using a higher dose of sotalol (100 mg in seven of eight patients), found a significant increase in both the effective refractory period of the ventricle (248±24 to 276±21 ms ($p<0·001$)), and in monophasic action potentials measured using special suction electrodes positioned in the right ventricular apex (248±18 to 290±29 ms ($p<0·01$)). Echt *et al.*[30] recently reported that sotalol, and not propranolol, prolonged atrial and ventricular refractory periods, and also the monophasic action potentials. Both groups agreed with Singh and Vaughan Williams[4] that sotalol differed significantly from other beta antagonists. The present study has confirmed that sotalol causes a moderate prolongation of the atrial and the ventricular effective refractory periods. Accessory pathway refractoriness also increased in both the anterograde and retrograde direction, an effect that has not been noted with other beta antagonists.[31]

In this study, and that briefly reported by Echt and colleagues,[30] sotalol significantly prolonged the QT interval measured during sinus rhythm. The QT interval assessed during identical rate atrial pacing was also increased by sotalol, but this has not been the case with propranolol.[32] The prolongation of the QT was confined to the JT interval as the QRS complex width did not prolong. In the present study the QTc lengthened very slightly but this change was not significant. Bazett's correction of the QT interval (QTc) was formulated to allow for physiological variation in heart rate, and is of uncertain value in pharmacological studies. Neuvonen *et al.*,[33] however, have demonstrated an approximately linear relation between QTc prolongation and serum sotalol concentration. In addition, a number of investigators have shown dramatic increases of the QT and QTc intervals associated with sotalol intoxication and in several instances this has been associated with ventricular arrhythmias (torsade de pointes).[34-36]

The effects of sotalol on the ventricular and accessory pathway effective refractory periods and on the QT and JT intervals are not typical of beta adrenergic antagonists, but are seen with other drugs which prolong the action potential and are consistent with additional class III action. Similar electrophysiological and proarrhythmic effects have been found with the prototype class III agent, amiodarone.[37-39]

The efficacy of sotalol, however, when given during established atrioventricular re-entrant tachycardia in this study is disappointing. Though tachycardia slowed in all patients it terminated in only five, with termination occurring in the anterograde direction. Furthermore, the tachycardia atrioventricular interval prolonged to a greater extent than the ventriculoatrial interval, suggesting a predominantly atrioventricular nodal effect.

Sotalol shows the electrophysiological effects of a class III antiarrhythmic agent as well as those of a competitive beta receptor antagonist, but the relevance of these findings to clinical practice requires further evaluation.

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Acute prolongation of myocardial refractoriness by sotalol

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SUMMARY Sotalol, a beta adrenoceptor antagonist, was given intravenously to 15 patients with accessory atrioventricular pathways during intracardiac electrophysiological studies. Eleven patients had the Wolff-Parkinson-White syndrome and four patients had concealed left sided accessory pathways. Four patients were restudied while receiving oral sotalol.

In contrast to the actions typical of beta blocking agents, intravenous sotalol prolonged the effective refractory periods of the ventricles and accessory pathways and reduced the ventricular response to atrial fibrillation in the patients with the Wolff-Parkinson-White syndrome. Similar results were obtained with oral administration.

These findings support the observation that sotalol, unlike other beta blocking agents, causes acute prolongation of the myocardial action potential and suggest that this action might be of therapeutic use.

In 1970 Singh and Vaughan Williams[1] showed in vitro that sotalol, unlike other beta adrenoceptor antagonists, prolonged the action potential of the myocardial cell. This effect, designated "class III" in their classification of antiarrhythmic actions, is also possessed by amiodarone,[2 3] raising the possibility that sotalol might have important antiarrhythmic actions not associated with other beta blocking agents.

Only recently has it been shown that sotalol prolongs the myocardial action potential duration in man: in eight patients with chronic atrial fibrillation the drug given intravenously in a dose of 40 to 100 mg prolonged ventricular repolarisation by 13 to 17%.[4] Ward *et al.*,[5] however, using a smaller dose of 0·4 mg per kg body weight were unable to show significant prolongation of the ventricular effective refractory period and concluded that sotalol only had electrophysiological actions typical of all beta blockers, that is depression of sinus node automaticityy and atrioventricular nodal conduction.[6]

In this study patients with an accessory atrioventricular pathway either overt (that is Wolff-Parkinson-White syndrome) or concealed[7 8] were selected for study because they provided two indices, ventricular and accessory pathway refractoriness, which should be affected by a class III drug but not by beta adrenoceptor blockade[5 7 9] (myocardial refractoriness may also be prolonged by membrane stabilising drugs[7] but sotalol does not have this property[1]). In the patients with Wolff-Parkinson-White syndrome the effect of sotalol on a third variable, the ventricular response to atrial fibrillation, was also assessed. In the Wolff-Parkinson-White syndrome, atrial fibrillation cannot usually be controlled by drugs which depress atrioventricular nodal conduction because in most cases the majority of atrial impulses are conducted to the ventricles via the accessory pathway.[7] The ventricular response can be very rapid and may thereby cause ventricular fibrillation; most episodes of ventricular fibrillation occur in patients in whom the shortest interval between pre-excited ventricular complexes during atrial fibrillation is less than 205 ms.[7] Measurement of this interval has been used to assess the effect of drugs on the accessory pathway[10 11] and provides the opportunity to see whether sotalol, like amiodarone,[12] can be effective in controlling an arrhythmia which will not respond to beta adrenoceptor blockade.[7 9]

Patients and methods

Fifteen patients prone to paroxysmal tachycardia, aged 19 to 63 years, were studied. Eleven had the Wolff-Parkinson-White syndrome (five type A and six type B) and four had concealed left sided accessory atrioventricular pathways. Diagnoses were based on

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standard electrophysiological criteria[7,8] and informed consent was obtained. Antiarrhythmic drugs were stopped at least 72 hours before study and, in two patients who had failed to respond to amiodarone, therapy was discontinued three months beforehand.

Electrograms from the lateral right atrium, septal region of the right atrium, bundle of His, and left atrium were recorded simultaneously via transvenous electrodes which were introduced into the right femoral and a left antecubital vein under local anaesthesia and advanced to the right atrium, tricuspid valve region, right ventricular apex, and coronary sinus, respectively.[13] Surface leads I, II, and VI were also recorded. Recordings were made by means of a six channel electrocardiograph recorder at a paper speed of 100 mm/s.

The effective refractory periods of the atria, ventricles, and accessory pathway were measured by the extrastimulus technique[13] using a programmable stimulator. Atrial and ventricular effective refractory periods were defined as the longest coupling intervals of atrial or ventricular extrastimuli which did not result in atrial or ventricular depolarisation, respectively. The effective refractory period of the accessory atrioventricular pathway in the anterograde direction was defined as the longest coupling interval of an atrial extrastimulus which resulted in atrial activation but failure of conduction over the accessory pathway and hence loss of delta wave. The effective refractory period of the accessory pathway in the retrograde direction was defined as the longest coupling interval of a ventricular extrastimulus which failed to be conducted to the atria by the accessory pathway as judged from absence of eccentric atrial activation and/or abrupt increase in ventriculoatrial conduction time.

Where possible, atrioventricular re-entrant tachycardia was initiated and terminated by precisely timed premature atrial or ventricular stimuli.[13] In the patients with Wolff-Parkinson-White syndrome, atrial fibrillation was initiated by rapid atrial pacing.[7]

Measurements were repeated 10 to 20 minutes after the completion of an infusion of sotalol hydrochloride, 1·5 mg per kg body weight, given over five minutes. This dose was used because it is in the same order of magnitude as the recommended oral dosage (the bioavailability of sotalol is almost 100%[14]). Four patients were restudied after an interval of two days, three weeks, 10 weeks, or 12 weeks after treatment with oral sotalol had been started (160 mg twice daily).

Results

INTRAVENOUS SOTALOL

The drug did not cause any unwanted effects.

The effective refractory periods of the atria, ventricles, and accessory pathways were prolonged by sotalol and both the cycle length during atrioventricular re-entrant tachycardia and the minimum interval between pre-excited beats during atrial fibrillation were increased. In three patients sotalol was given during atrial fibrillation. The ventricular rate slowed two minutes after the injection but sinus rhythm did not return for six, 12, and 18 minutes, respectively. The results from patients where measurements could be made both before and after intravenous sotalol are summarised in the Table and in Fig. 1–6.

It was not possible to obtain complete data in all patients. In seven patients, atrial refractoriness exceeded refractoriness of the accessory pathway in the anterograde direction, preventing measurement of the latter. Similarly, in three patients measurement of the effective refractory period of the accessory pathway in the retrograde direction was not possible because it was less than the ventricular effective refractory period. In three patients, premature atrial stimulation initiated atrial fibrillation, preventing measurement of the atrial effective refractory period. Atrial fibrillation persisted in two patients, preventing measurement of the effective refractory periods of the ventricles and accessory pathway. Atrial refractoriness was not measured in two patients because atrial stimulation repeatedly induced atrioventricular re-entrant tachycardia. Atrioventricular re-entrant tachycardia could not be initiated in five patients

Table *Mean values and standard deviations of effective refractory periods, cycle lengths during AV re-entrant tachycardia (AVRT) and minimum interval between pre-excited ventricular complexes during atrial fibrillation (RR_{min}) in milliseconds before and after intravenous sotalol*

	Effective refractory periods				*AVRT*	RR_{min}
	Atria	*Ventricles*	AP_{AV}	AP_{VA}		
Before	224±37	209±23	297±75	295±50	372±68	268±77
After	264±49	245±20	360±75	349±65	423±64	351±63
No.	10	13	3	11	6	11
p	<0·002	<0·002	<0·01	<0·002	<0·05	<0·002

No., number of patients with data before and after sotalol; p, significance level determined by Wilcoxon's signed ranks test; AP_{AV} and AP_{VA}, refractory periods of accessory pathway in anterograde and retrograde directions, respectively.

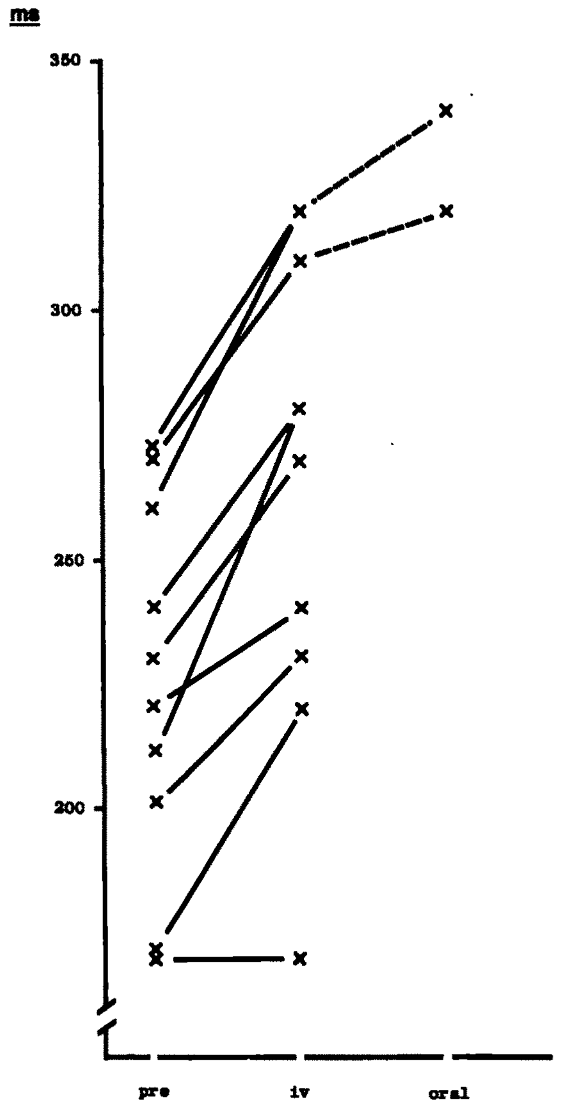

Fig. 1 *Atrial effective refractory periods before (pre), after intravenous (iv) and oral sotalol.*

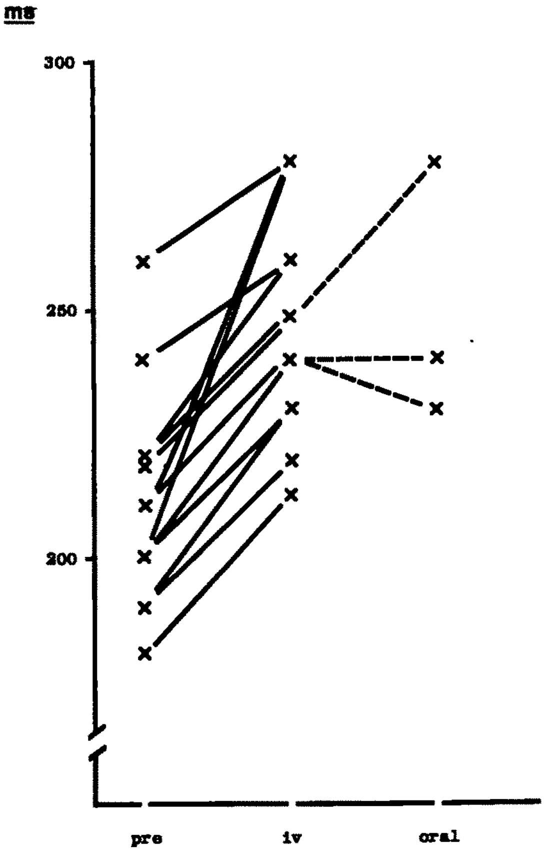

Fig. 2 *Ventricular effective refractory periods before (pre), after intravenous (iv) and oral sotalol.*

before or after sotalol and in a further four patients after sotalol had been given.

ORAL SOTALOL

Electrophysiological measurements after oral sotalol were similar to those after intravenous administration (Fig. 1–6). Atrial fibrillation occurred in two patients, preventing measurement of atrial refractoriness in both, and anterograde accessory pathway refractoriness in one. In two patients, atrial refractoriness exceeded that of the accessory pathway in the anterograde direction, precluding measurement of the latter. In one patient ventriculoatrial conduction was blocked by oral sotalol. Technical difficulties in recording an atrial electrogram during ventricular pacing prevented measurement of retrograde accessory pathway refractoriness in one patient.

Discussion

This study shows that, in contrast to other beta blocking drugs,[5 9] sotalol acutely prolongs ventricular and accessory atrioventricular pathway refractoriness, thereby supporting the in vitro[1] and in vivo[4] observations that sotalol, in addition to being a beta adrenoceptor antagonist, prolongs the duration of the myocardial action potential. Atrial refractoriness was also prolonged but this action is not unique to sotalol: atenolol[15] and pindolol[16] also prolong the atrial effective refractory period though the mechanism is not clear.[5]

That sotalol has electrophysiological actions in

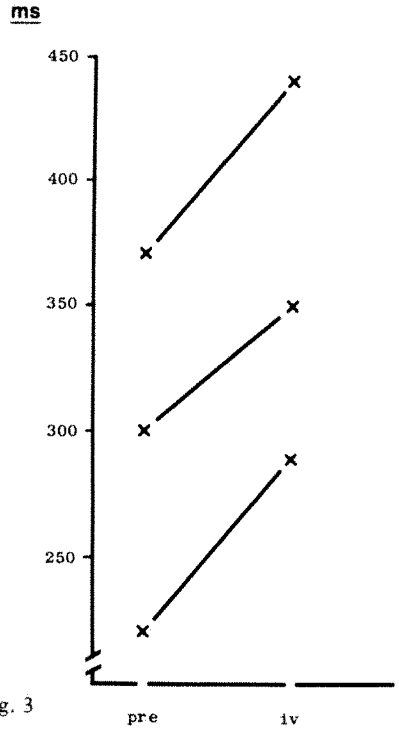

Fig. 3

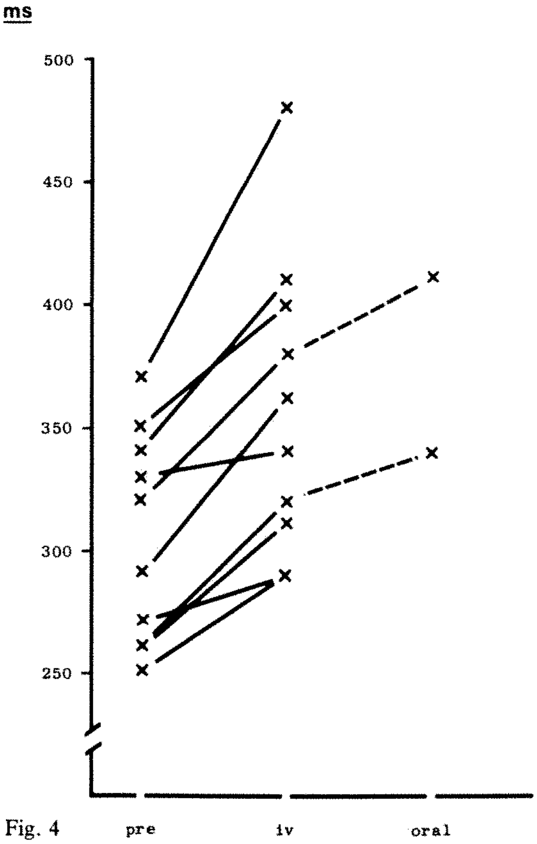

Fig. 4

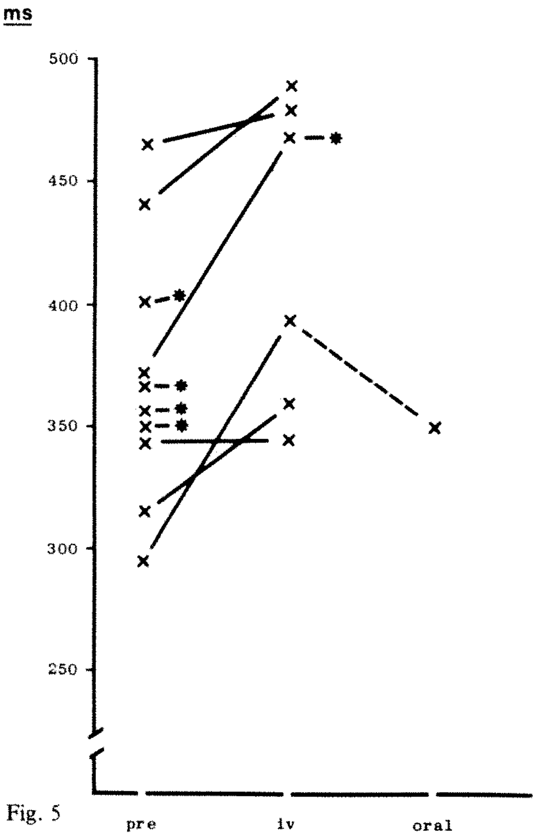

Fig. 5

Fig. 3 *Effective refractory periods of the accessory pathway in the anterograde direction in three of the patients with Wolff-Parkinson-White syndrome before (pre) and after intravenous (iv) sotalol.*

Fig. 4 *Effective refractory periods of the accessory pathway in the retrograde direction before (pre), after intravenous (iv) and oral sotalol.*

Fig. 5 *Cycle length during atrioventricular re-entrant tachycardia before (pre), after intravenous (iv) and oral sotalol. An asterisk indicates that sotalol prevented initiation of tachycardia.*

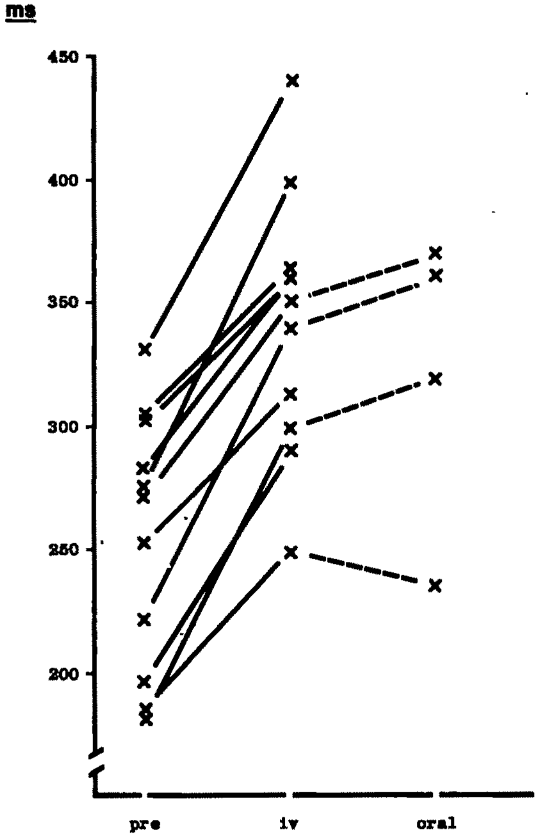

Fig. 6 *Minimum interval between pre-excited ventricular complexes during atrial fibrillation in patients with Wolff-Parkinson-White syndrome before (pre), after intravenous (iv) and oral sotalol.*

common with amiodarone suggests that it might have important antiarrhythmic properties other than those resulting from beta adrenoceptor blockade. A large trial comparing the clinical antiarrhythmic effects of sotalol with another beta blocking agent is required to answer this question. The reduction of ventricular rate during atrial fibrillation in the patients with Wolff-Parkinson-White syndrome with both intravenous and oral sotalol does, however, demonstrate that the drug can be effective in the treatment of an arrhythmia which will not respond to beta adrenoceptor blockade.[7] Furthermore, prolongation by sotalol of refractoriness of the accessory pathway, which forms the retrograde limb in many atrioventricular re-entrant tachycardias,[7] may be useful in the prophylaxis of this arrhythmia.

Recently, metoprolol has been shown to prolong myocardial action potential duration in man after chronic, but not acute, administration.[17] The same phenomenon has been shown in rabbits with several beta blocking drugs.[18] Even though chronic beta blockade may confer a class III effect it does not, however, lead to the same impressive antiarrhythmic efficacy as amiodarone.[3] Either the efficacy of amiodarone results from actions other than its class III effect or, more probably, there are quantitative differences between the class III actions of chronic beta blockade and amiodarone.

One mechanism by which amiodarone is thought to be effective is by uniformly prolonging action potential duration throughout the myocardium and thereby reducing the heterogeneity of action potential duration which can predispose to ventricular arrhythmias.[19] Sotalol may well have a similar action but it should be noted that there have been a number of reports of ventricular arrhythmias being caused by extremely high doses of sotalol.[20]

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Myocardial disarray
A critical review

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SUMMARY Myocardial disarray or disorganisation is at present a contentious topic, not least because its value as a clinical marker for hypertrophic cardiomyopathy has changed considerably over the years. Initially observed as one of the features of asymmetric septal hypertrophy, disarray has since been promoted as its pathognomonic histological feature, regarded by some observers as the morphological manifestation of a genetically transmitted myocardial defect. Recently, however, it has become evident that myocardial disarray is not limited to hypertrophic cardiomyopathy, but is encountered in hearts with both congenital and acquired conditions, and is also observed in normal hearts. The specificity of disarray for hypertrophic cardiomyopathy is thus seriously questioned. Latterly, it has been suggested that disarray, judged from through-and-through sections of the ventricular midseptum, is a highly specific and sensitive marker of hypertrophic cardiomyopathy when considered in *quantitative* rather than *qualitative* fashion.

The present study sets out to answer the question whether disarray could be the histological expression of the normal but intricate fibre architecture of the heart, a consideration also initiated by debatable definitions of normality and abnormality of myocardial histology. Gross fibre dissections in five normal hearts showed that many sites occurred in which disarray was a natural phenomenon. In five more hearts it was found that the plane of section of a tissue block might profoundly influence the histology. In fact, tissue cubicles sampled from different faces showed a change in histology in the vast majority. Thus the diagnostic significance of myocardial disarray as a marker of hypertrophic cardiomyopathy in the clinical setting almost vanishes; a change in orientation of a tissue section may actually turn "normality" into "disarray".

The diagnosis of hypertrophic cardiomyopathy is based on a number of criteria of which asymmetric septal thickening, myocardial disarray, and systolic anterior movement of the anterior papillary muscle of the mitral valve are considered of prime importance.[1] Indeed, for clinicians and pathologists alike the diagnosis is often easily made, not least because of the obvious asymmetrical wall thickening. Septal asymmetry and a bizzarre myocardial texture are not, however, always present. Moreover, the disease is not necessarily obstructive. Furthermore, it has been shown unequivocally that hypertrophic cardiomyopathy can occur under divers clinical conditions and it has thus been suggested that the disease does not represent a distinct entity, but instead a final common pathway.[2] It is on the basis of these uncertainties in finding definitive criteria for the diagnosis that in recent years much emphasis has been put on histological features, collectively termed myocardial disarray or disorganisation. In fact, myocardial disarray, in isolation, has been considered a "highly specific and sensitive marker" of hypertrophic cardiomyopathy.[3-5] In our experience, however, the torrent of articles solely concerned with myocardial disarray has led to misconceptions regarding the interpretation of this histological feature. It is our purpose, therefore, to review the evolution of myocardial disarray in the articles published in an attempt to reappraise its value as a diagnostic tool in hypertrophic cardiomyopathy.

Historical review

Over recent decades the concept of myocardial disarray underlying ventricular dysfunction has excited

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cardiologists. Teare's observations in 1958[6] that sudden death (in eight of nine patients) was associated with asymmetric septal hypertrophy, histologically characterised by a bizarre myocardial fibre architecture and conspicuous interstitial fibrosis, set the scene for relating myocardial disarray to this condition. Indeed, myocardial disarray was considered an important feature, but almost all investigators stated that when taken in isolation it was non-specific.[7-11]

For that very reason, Van Noorden and coworkers[12] introduced a semiquantitative approach to diagnosis, which included other histological features such as the degree of hypertrophy and fibrosis. In this way they hoped to improve the specificity of the histological diagnosis of asymmetric septal hypertrophy.

Subsequent investigators, however, have singled out myocardial disarray as the pathognomonic histological feature.[13] Some have gone so far as to consider myocardial disorganisation as the morphological manifestation of a genetically transmitted myocardial defect.[14-16] In the mean time, it became evident that most conditions unified clinically by "idiopathic" hypertrophic cardiomyopathy presented with signs of failure of left ventricular compliance rather than with outflow obstruction.[17 18] The promoters of disarray as the specific histological feature for asymmetric septal hypertrophy then modified their concept by stating that hearts with obstruction had myocardial disarray confined to the thickened subaortic septal area, while hearts without obstruction presented disarray in a diffuse manner throughout the ventricular free wall.[14 15] The universality of this concept was soon disproved, not only by some of the cases reported by the same authors,[14 19] but also by the well documented study of Edwards and co-workers.[20]

The matter became further complicated when it was shown that asymmetric septal thickening, accompanying both acquired and congenital anomalies, could occur also in the absence of myocardial disarray.[21] For these cases yet another term was introduced, viz. "disproportionate septal thickening" so as to distinguish these cases from those with both septal thickening and myocardial disarray (see for reviews Maron and Epstein[1 22]). The distinction was deemed necessary since the conditions that possessed disarray presented a familial trait, while the septal thickening in the cases without disarray was considered a secondary phenomenon accompanying other diseases.

At this stage the waxing interest in hypertrophic cardiomyopathy and the possible role of myocardial disarray as its pathological substrate had led other investigators into the arena (see for reviews[1 23-26]). It became evident that disarray was not confined to hypertrophic cardiomyopathy, but was seen in a variety of conditions including normal hearts. The specificity of myocardial disarray for hypertrophic cardiomyopathy was seriously questioned, if not denied, thus reinforcing the opinion of the earlier investigators (see above). For example, Jones and associates[27] showed that the tissue specimens surgically removed from the hypertrophic infundibula in Fallot's tetralogy contained myocardial disarray indistinguishable from that present in hearts with asymmetric hypertrophy. Interestingly enough this work was presented by the same group of senior investigators who had promoted the concept that myocardial disarray was a *specific* marker for asymmetric septal hypertrophy. Van der Bel-Kahn[28] documented the presence of myocardial disarray in a variety of conditions, such as systemic hypertension, cor pulmonale, coronary heart disease, and normal hearts. Compared with hearts with hypertrophic cardiomyopathy the disarray encountered was similar from a histological point of view, but less extensive. Bulkley and coworkers[29 30] documented myocardial disarray in fetal and infant hearts and in some types of congenital heart disease, such as Fallot's tetralogy and aortic and pulmonary atresia with intact ventricular septum. Beçu and associates[31] described similar findings in hearts with isolated pulmonary valve stenosis.

These observations in congenital lesions, which incidentally could not be verified by Maron and his group of investigators,[32] led Bulkley and associates[29] to hypothesise that the force distribution within the myocardium could play a role in the development of myocardial disarray, a concept further expanded by Hutchins and Bulkley[33] to encompass hearts with "classical" asymmetric septal hypertrophy. This point of view has recently received further support from the observation that myocardial disarray also developed in papillary muscles released from normal tension after mitral valve replacement.[34]

The overwhelming evidence that myocardial disarray was not confined to hearts with hypertrophic cardiomyopathy has led to further studies by the Bethesda workers, who now claim that myocardial disarray is a highly sensitive and specific marker for hypertrophic cardiomyopathy only when considered in a *quantitative* rather than a *qualitative* fashion.[3 4] In making their quantitative judgment, however, they excluded all the tissue sections from areas other than the ventricular septum. Moreover, they based their quantitative assessment solely on through-and-through midseptal sections cut in a transverse plane. St John Sutton and colleagues[35] recently also showed that myocardial disarray was more extensively present in the hearts of patients with hypertrophic obstructive cardiomyopathy compared with that in normal hearts or in those of patients with congestive cardiomyopathy or aortic stenosis. These authors also used full thickness sections, but they did not mention the restrictions in sampling introduced by the

Bethesda group. Furthermore, St John Sutton and his colleagues[35] concluded that in hearts with obstructive hypertrophic cardiomyopathy myocardial disarray did not differ much among sections from the ventricular septum or the left ventricular free wall and, moreover, appeared independent of septal and free wall thickness. Still more recently, Maron and co-workers,[5] expanding on their earlier material, endorsed the work of St John Sutton *et al.*[35] and now concluded in addition that in patients with hypertrophic cardiomyopathy, not necessarily obstructive, the left ventricular free wall—when sectioned transversely—also contained more extensive disarray than it did in their reference cases. They suggested on the basis of these findings that myocardial disarray "may represent a diffuse cardiomyopathic process", probably congenital in nature.[5 25] It is interesting, therefore, that St John Sutton and his colleagues,[35] on almost the same findings, concluded that myocardial fibre disarray "probably represents an exaggeration of a non-specific common pathway for many divers pathophysiological processes".

The overall conclusion reached at present is that disarray is more extensively present in hearts with hypertrophic cardiomyopathy than in other conditions. This in itself is hardly a revelation, since the whole subject of myocardial disarray came into focus because it was such a striking feature in hearts with asymmetric septal hypertrophy. The practical value of myocardial disarray as a diagnostic marker, however, has almost vanished, since the criteria for evaluation cannot readily be fulfilled in a clinical setting! Indeed, the limited diagnostic value of small pieces of tissue, obtained either with endomyocardial biopsy or during septectomy, has already been shown.[36-38] Thus, we are left with a dilemma of how to interpret myocardial disarray in ordinary histological sections, which is particularly pressing since it has unequivocally been shown that disarray can occur in hearts without any sign of myocardial dysfunction. In such cases one may wonder whether disarray represents a congenital derangement of myocardial architecture and, hence, an abnormality, or is the histological expression of a myocardial fibre architecture which can be basically normal. The latter possibility would at least explain why so many areas have to be excluded from histological evaluations in diagnosing hypertrophic cardiomyopathy.

Indeed, Streeter[39] and Ross and Streeter[40] suggested that the occurrence of myocardial disarray could be the simple consequence of gross fibre architecture; Fujiwara and associates[41] also indicated that myocardial fibre disarray in their sections corresponded to fascicle disarray in thick sections.

In the light of these developments we have re-evaluated the histology of the myocardium so as to investigate the occurrence of myocardial disarray at different sites in normal hearts, taking gross muscle fibre orientation as the point of departure.

Preparation of normal hearts

Ten normal hearts from patients who died of diseases unrelated to the cardiovascular and/or pulmonary system were examined. Five were studied by gross dissection of the myocardial fibres. These hearts came from patients, 1 day, and 2, 15, 18, and 75 years of age, respectively. All specimens were fixed in formalin. The dissection was carried out after removal of atria and stripping of the epicardium, fat, and the extramural coronary arteries. In two hearts (the 1 day and 15 year old cases) the myocardium was dissected using artificial cleavage planes, according to a method described by Lev and Simkins.[42] The three remaining hearts were dissected using a step by step technique, stripping off myocardial fibres with the atrioventricular annuli as points of departure. The same sequence was followed throughout the procedures in the different specimens. Each step was photographed so that the fibre orientation could be critically compared between different hearts.

The remaining five hearts were used for a microscopical survey. These hearts came from patients 1 day, 4 months, and 4, 9, and 21 years of age. All hearts were fixed in formalin. Twelve full thickness blocks were removed for histological study (Fig. 1). The first two blocks were taken from the ventricular septum and adjacent anterior left ventricular free wall, approximately 1 cm beneath the aortic valve (Fig. 1A). Nine blocks came from a transverse slice through the heart taken approximately halfway between base and apex (Fig. 1B). The final block was taken from the left ventricular apex (Fig. 1A). Each block was removed as a cube varying from approximately 5 mm in small hearts to about 15 mm in larger hearts. All blocks were embedded in paraplast and routinely processed. Each block was then cut sequentially in three different planes, re-embedding being necessary for each of the three cuts. The first sections from each block were taken in a plane perpendicular to the long axis of the heart, that is in a transverse plane relative to the block. For the second series of sections each block was re-embedded in such a way that all blocks taken from the ventricular free walls and the anterior and posterior septal insertions were cut in a plane parallel to the endocardium. The remaining blocks from the septum and ventricular apex were cut in the frontal plane, using the anterior aspect of the block as the target. A third plane of sectioning was then parallel to the remaining uncut third pair of faces of the cube. The three different planes of sectioning were tabulated as A, B, and C,

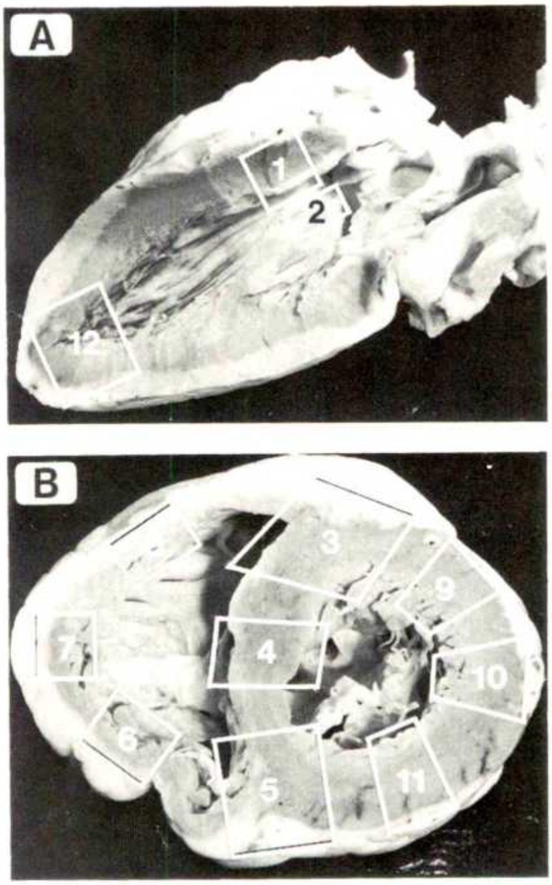

Fig. 1 *The sites of the 12 full thickness blocks removed for the histological study.*

respectively.

All sections were cut at 10μ thickness and stained with haematoxylin and eosin. A total number of 180 sections was studied: one section from each of the three faces of the 12 blocks in the five hearts.

DEFINITION OF HISTOLOGICAL CRITERIA

Because of the aforementioned controversies regarding the differentiation of "disorganisation" from normality we have tried to classify myocardial histology according to the criteria set by Maron and Roberts[3] and Maron *et al.*[4] Thus, we have tried to distinguish three basic arrangements. The first arrangement which Maron and associates[4] defined as normal, should be typified by a strictly parallel alignment of myocardial fibres (Fig. 2). The second arrangement, in which the cells did not show a rigid parallel alignment, was classified by them as a minor deviation of normality. It included different histological variants, such as branching myocardial cells and arrangements in which small fascicles of cells were cut transversely among other muscle cells cut in a more or less longitudinal fashion (Fig. 2). We found it impossible to apply these criteria in a strict sense, since close observation of so-called parallel alignment disclosed that cellular branchings were almost always readily identified. Thus, we have considered the histology only as "parallel" when the major proportion of myocardial cells showed a parallel alignment, irrespective of the presence or absence of branching.

Finally, we distinguished myocardial disorganisation, characterised by a more complex texture of myocardial cells (Fig. 3), of which these authors already indicated that it assumed a wide spectrum of morphological appearances. Maron and Roberts[3] and Maron *et al.*[4] distinguished two major forms, further subcategorised into five histological types in alphanumerical fashion. We experienced great difficulties in recognising the often subtle differences, particularly since the different types often merged in one and the same histological section. Hence, we have abstained from introducing an elaborate subdivision, while we are primarily interested in differentiating "normal" from "minor deviations of normality" from "disorganisation". Moreover, we have not expressed the various patterns as percentages of surface area of the section, but instead have labelled a section according to its dominant histological feature, viz. the feature that captured at least 50% of the total surface area of the section.

In other words, we have used their definitions, but we have simplified the issue. Nevertheless, it is important to note that these authors state that a particular configuration (their type I), characterised by perpendicular or oblique alignment of individual cells or bundles of cells, "exclusively involves areas of septum in which cardiac muscle cells were cut longitudinally" (Maron and Roberts[3]: p.691).

Results

GROSS FIBRE ORIENTATION

Greenbaum *et al.*[43] have recently reviewed and studied gross fibre orientation in normal hearts, emphasising regional variations in ventricular wall architecture of significance for ventricular function. Our present study has extended this investigation to examine possible sites of microscopical disarray.

Like Greenbaum *et al.*[43] we were able to distinguish subepicardial, middle, and subendocardial layers, at the same time confirming their statement that these layers could not be considered distinct entities. Indeed, the concept of discrete muscle bundles spiralling through the ventricular walls and the septum previously has been discarded,[42,44] emphasising the intricacy of the myocardial fibre arrangements, a gen-

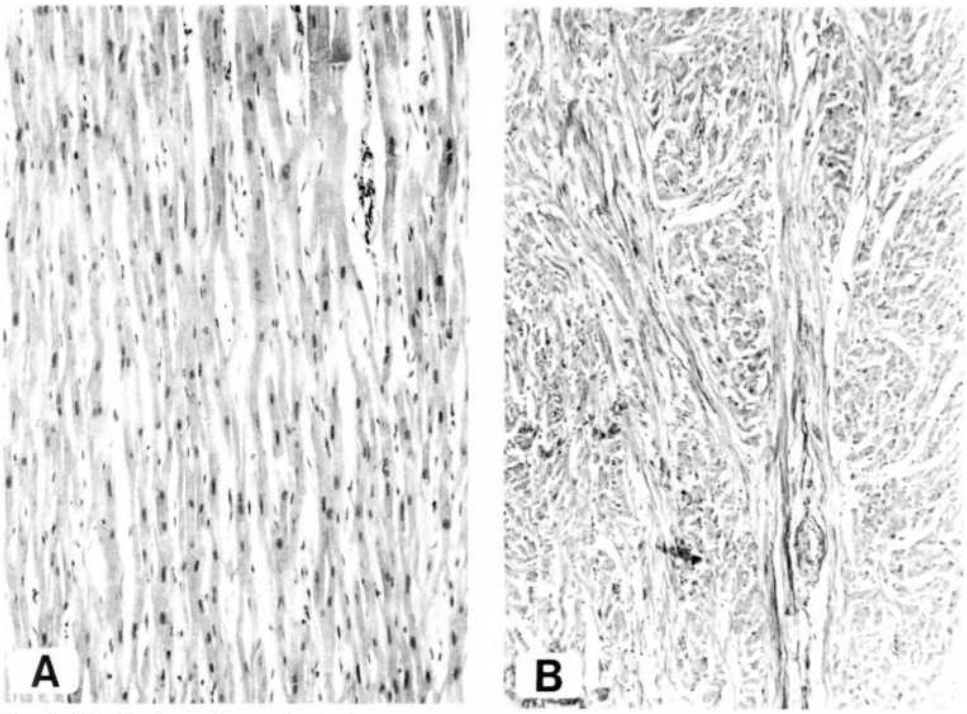

Fig. 2 *The histology of "normality", characterised by a parallel alignment of myocardial fibres (A), and an example of a "minor deviation of normality" (B), according to the definitions set by Maron and co-workers.*[3 4] *(Haematoxylin and eosin stains; original magnifications (A) ×140; (B) ×90.)*

erality important to recall when considering myocardial fibre texture in histological sections.

The distinction between the layers is largely based on the observation that the orientation of the fibres in what is called a layer changes less rapidly with depth than orientations encountered in a considerably deeper level of dissection (Fig. 4). Hence, the interfaces between these layers are not clearly demarcated.

Other regions of interdigitating myocardial fibres are the interventricular sulci and the right anterior atrioventricular groove (Fig. 4). The slightly deeper layers of the subepicardial zone dip into the middle layer and contribute to the formation of the main muscle mass of the ventricular septum. In doing so, these fibres intermingle with those of the middle layer and the fibre constituents derived from the right ventricular free wall. This architecture is more outspoken along the anterior interventricular sulcus than it is posteriorly, but at both sites gross fibre disarray is present as a natural phenomenon.

In the mature heart the greater part of the septum is composed of the left ventricular middle layer. The midseptal aspect, therefore, will contain muscle with its main fibre direction more or less perpendicular to the long axis of the left ventricular (Fig. 5), while the subendocardial layers on both sides show longitudinal and oblique fibre directions.

The posterior aspect of the aortic annulus gives rise to fibres that also penetrate into the ventricular septum and run down almost in the long axis of the heart, intermingling with those that form the main septal muscle mass (Fig. 5). From the left anterior aspect of the aortic annulus, fibres arise which run parallel to those derived from the adjacent area of the mitral annulus. These fibres intermingle with the subepicardial fibres of the right ventricle which have bridged the anterior interventricular sulcus.

Likewise, gross fibre disarray is present at the ventricular apices. Subepicardial fibres from both the right and left ventricular vortices turn inward and continue into the subendocardial layers and papillary muscle groups (Fig. 5). The ventricular apices, therefore, show a rapid transition of the subepicardial "swirling" fibres into the almost longitudinal direction of fibres in the subendocardial trabeculae. A middle layer is missing from these areas. This arrangement also affects the architecture of the ventricular septum in its apical aspect.

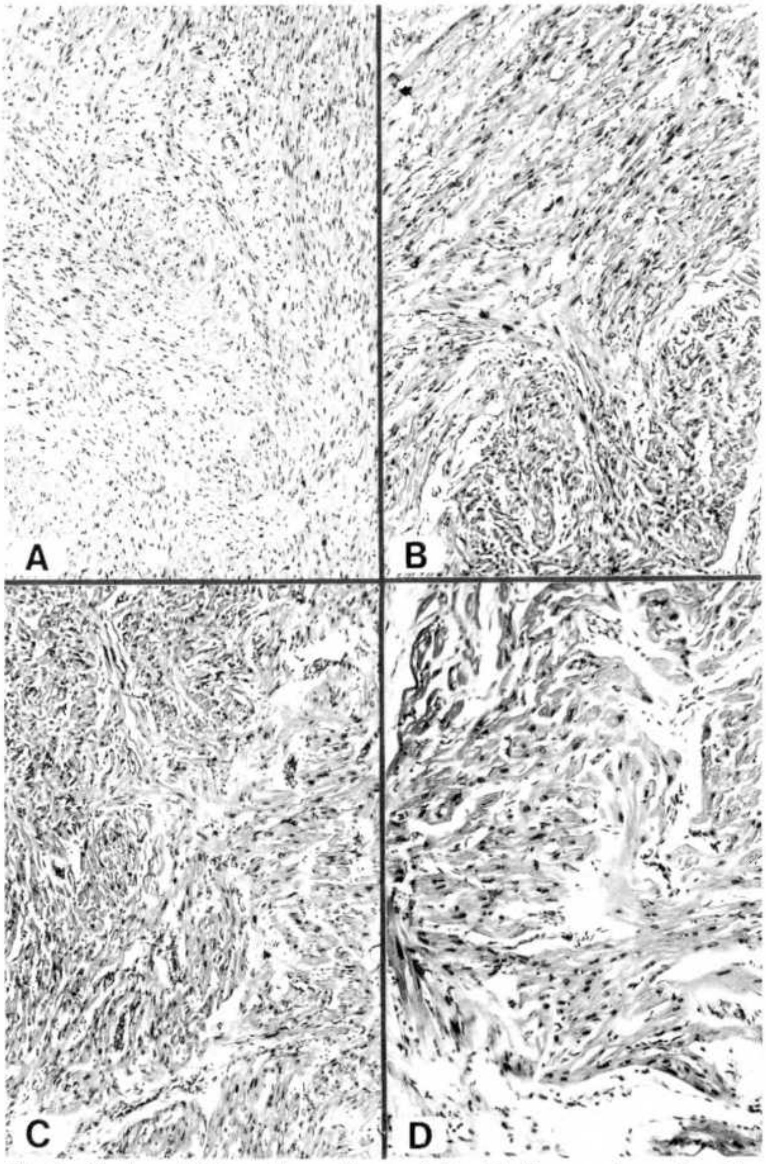

Fig. 3 *Histology of "disarray", according to criteria set by Maron and co-workers.*[34] *(Haematoxylin and eosin stains; original magnifications (A-C) ×90; (D) ×140.)*

A distinct difference is present in architecture between right and left ventricles. In contrast to the left ventricular wall the right ventricular free wall contains subepicardial and subendocardial layers which are closely packed together without much of a middle layer. The thin walled right ventricle will therefore almost everywhere show crossings of myocardial fibres.

Thus, natural fibre disarray is a common feature in various sites, such as the subaortic septal region, the anterior and posterior junctional sites between the septum and the parietal wall, the subendocardial zones, the right ventricular free wall, and the ventricular apices.

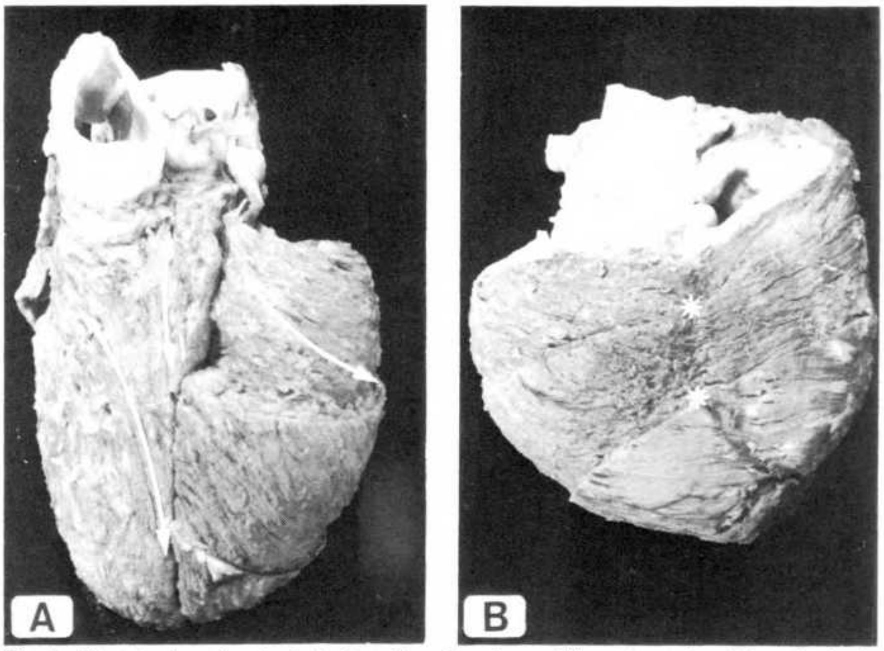

Fig. 4 *Heart specimen showing the intricate fibre orientation at different sites and at different levels of dissection. (A) Left anterior oblique view of the heart. The fibres that descend over the right ventricular outflow tract have an orientation different from the fibres that descend from the anterior aspect of the aortic root. Deeper dissection of the left ventricle shows yet another, more circular, arrangement (arrows). (B) The posterior aspect of the same specimen, shown with different levels of fibre dissection. The posterior interventricular groove (indicated by asterisks) shows an interdigitating fibre arrangement.*

HISTOLOGY OF NORMAL MYOCARDIUM

Of the 180 sections studied, using the aforementioned criteria, only 42 showed a parallel fibre arrangement (Table). In other words, on the basis of the criteria set by Maron and Roberts[3] and Maron *et al.*[4] only 23% of the sections were judged to show normal histology. Seventy-nine sections (44%) showed a minor deviation of normality, whereas disorganisation was present in 59 sections (33%). The distribution of these findings among the five hearts according to the site of the blocks and the plane of sectioning is given in the Table. Blocks 3, 4, and 5, derived from the midportion of the ventricular septum, showed minor deviations of normality in 20 sections, disarray in 17 sections, and a parallel alignment in only eight sections.

Changing the orientation of the block produced a change in the dominant microscopical appearance in 52 of the 60 blocks (Table). In only eight blocks were the same results produced irrespective of the plane of section. In six of these eight the histology was that of minor deviation, while in the other two there was unequivocal disorganisation. Thus, a strictly parallel arrangement was never observed in one block when sectioned in all three planes. In 15 blocks a different histology was found in each of the three planes (Fig. 6), while in the remaining 37 blocks a change in histology was found when sections were studied in two planes.

Discussion

In view of the confusion that surrounds the interpretation of myocardial disarray it is essential to appreciate that this review on myocardial disarray concerns the histology and its appraisal; it is not a dissertation of the histology in hypertrophic cardiomyopathy. In recent years various excellent reviews of the latter condition have been published.[1 23–26] There are, however, equally confusing reports regarding the importance of myocardial disarray as a histological feature, which some consider "highly specific and sensitive for hypertrophic cardiomyopathy", while others describe this texture in different conditions, including normal hearts. It is for these reasons, in particular, that we have focused on the normal heart.

The present study shows that areas with an inter-

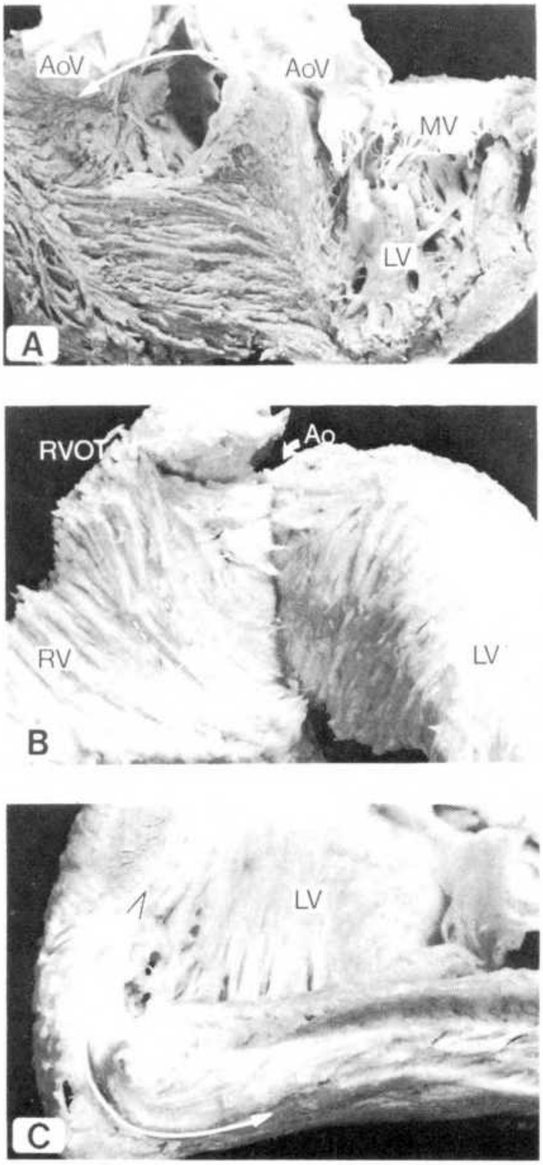

Fig 5 *Interdigitating fibre textures. (A) Heart speciman in which the interventricular septum has been dissected and opened like a clam (indicated by arrow). The part of the septum underneath the aortic valve (AoV) shows a very different fibre orientation, as compared with the more apical area. LV, left ventricle; MV, mitral valve. (B) Heart specimen in which the interventricular septum, separating the right (RV) from the left (LV) ventricle, has been opened by blunt dissection of the fibres. The main fibre orientation is indicated by dotted lines, showing extensive intermingling in the subaortic region. RVOT, right ventricular outflow tract; Ao, aortic root. (C) The apex of the left ventricle (LV) is dissected and shows the intricacies of the fibre orientations, such as subepicardial fibres that turn inwards (arrow) to continue in subendocardial position.*

weaving fibre architecture occur naturally in all normal hearts at several sites, including the ventricular septum. That this gross arrangement leads to cellular disarray at a microscopical level should therefore come as no surprise. Thus, when applying the criteria for deviations of normality and disarray, as promoted by Maron and co-workers,[3 4] it appears that of all tissue sections examined from five normal hearts almost 44% showed a "deviation of normality", and almost 33% showed "myocardial disarray". Thus a "normal" arrangement, according to the criteria set, occurred in only 23% of the sections. We may wonder what constitutes normality, particularly, since we then found that the plane of sectioning of the tissue blocks influenced the histology. Thus, in 87% of the blocks studied the histology changed when the orientation of the block was changed. In 38% of cases the alteration was from a parallel arrangement in one plane to disarray in another. In fact, in only eight of the 60 blocks was there no alteration, but none of these contained a parallel arrangement as the dominant histology.

What then is the significance of these findings regarding the specificity of myocardial disarray in diagnosing hypertrophic cardiomyopathy?

First we must conclude that random sections have limited value in this respect, a conclusion recently reached by Maron and his co-workers.[3 4 25] The main reason for this is that cellular disarray does indeed reflect fascicle disarray, as pointed out by Streeter,[39] and Ross and Streeter,[40] and Fujiwara and associates.[41] Greenbaum and associates[43] recently re-endorsed the intricacies of the gross fibre architecture of the heart, concluding that, within a basic framework, a uniform pattern is not present. Indeed, the fibre arrangement is such that areas are produced in which disarray occurs as a natural phenomenon. Our presentation has focused on this particular aspect and has unequivocally shown that such regions are widespread. These areas, such as the junctional sites between the ventricular free walls and the interventricular septum, the apices of the ventricles, the subendocardial regions, the right ventricular free wall, and the subaortic septal region, all stand out because of a "disorderly" arranged fibre geometry. It is of interest that these sites coincide with the areas that Maron and co-workers[3–5] have excluded from their recent studies on the specificity of myocardial disarray. Other workers, such as Van der Bel-Kahn,[28] Bulkley and associates,[29 30] and St John Sutton and associates[35] have also pointed out that areas with disarray are widely dispersed and occur in hearts with congenital and acquired diseases, as well as in normal hearts, both fetal and adult. Thus, we must indeed conclude that myocardial disarray in itself is a nonspecific feature; for its greater part it represents the

Table *Histological patterns obtained after sectioning each of three faces of 12 tissue cubicles sampled**

Case No.	*Age*	*Face of cubicle*	*Block No.* 1	2	3	4	5	6	7	8	9	10	11	12
1	Newborn	A	P	MD	D	MD	D	D	MD	MD	MD	MD	MD	D
		B	MD	D	MD	MD	MD	MD	P	P	MD	MD	P	P
		C	D	D	P	P	D	MD	D	D	MD	P	P	D
2	4 mth	A	MD	MD	D	D	D	MD	MD	MD	D	MD	D	D
		B	D	D	MD	P	D	MD	MD	D	D	P	D	MD
		C	MD	MD	P	MD	P	MD	D	P	P	P	P	MD
3	4 y	A	MD	P	MD	MD	D	MD	MD	MD	MD	D	D	D
		B	MD	MD	MD	MD	MD	P	P	P	MD	MD	D	MD
		C	MD	D	P	MD	D	MD	D	MD	P	P	MD	P
4	9 y	A	D	D	D	MD	D	MD	MD	P	D	MD	MD	D
		B	MD	MD	D	MD	P	P	P	D	P	P	P	D
		C	MD	D	D	MD	D	D	D	D	D	D	P	MD
5	20 y	A	MD	D	MD	MD	D	P	MD	MD	P	D	D	MD
		B	MD	D	MD	P	D	MD	P	P	MD	P	P	MD
		C	D	D	D	MD	MD	MD	P	P	MD	D	MD	MD

*See text: material and methods.

The histological patterns have been designated according to the criteria set by Maron *et al.*[3 4]: P, parallel arrangement; MD, minor deviation of normality; D, disarray (see also "definition of histological criteria").

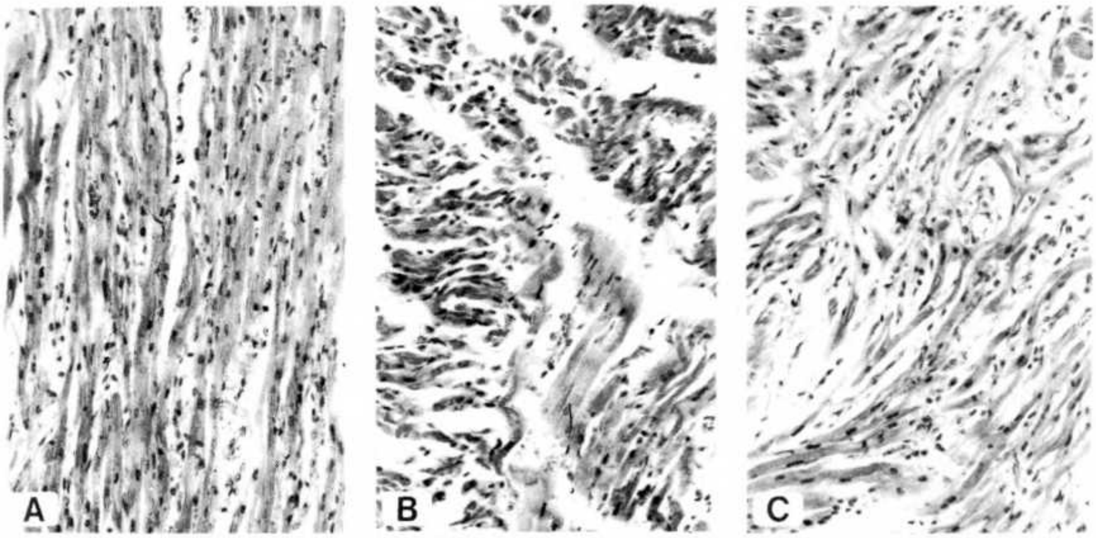

Fig. 6 *The dominant histology after sectioning the three faces of one of the tissue cubicles. (A) "Parallel" fibre arrangement; (B) "minor deviation of normality"; (C) "disarray". (Haematoxylin and eosin stains; original magnification ×230.) (Reproduced from Becker A E and Caruso G. In:* Paediatric cardiology *Vol. 3, 1981, p 317; by permission of Churchill Livingstone.)*

histological counterpart of gross fibre arrangement.

The question then remains as to how specific the myocardial disarray is for hypertrophic cardiomyopathy when it is present in the midseptal area?

The recent works of Maron and associates[3 4] suggest that extensive occurrence of disarray in the ventricular midseptum is a "highly specific and sensitive marker for hypertrophic cardiomyopathy", though the authors also report some instances without disorganisation despite the fact that these cases clinically were indistinguishable from the others.[25] In other words, in keeping with our own experiences, myocardial disarray is not per se a feature of hypertrophic cardiomyopathy and its absence, therefore, does not exclude the diagnosis. When present, however, disarray in over 5% of the total surface area of through-and-through sections of the midseptum is considered diagnostic for hypertrophic cardiomyopathy. We

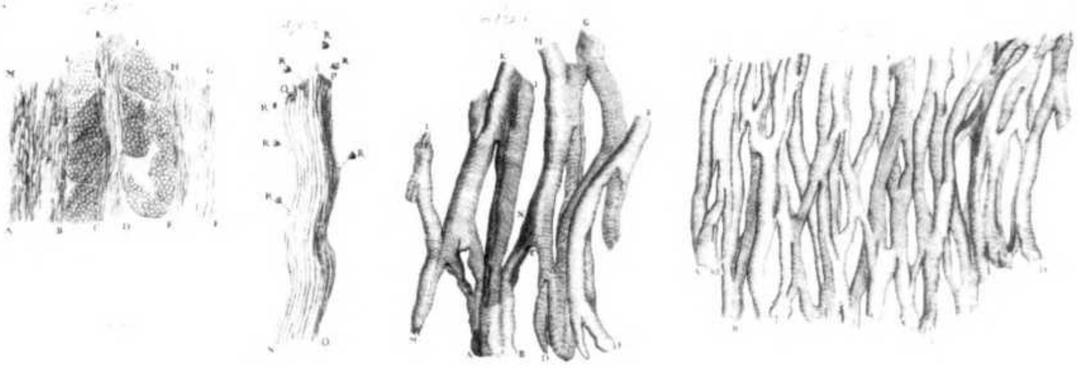

Fig. 7 *Antoni van Leeuwenhoek's drawings of the myocardium of the duck from his correspondence (letter No. 82) with the members of the Royal Society, London, April 1694. (Courtesy of Dr J James, Professor of Histology, University of Amsterdam.)*

may, of course, challenge the practical significance of this approach in the clinical context, but nevertheless it is indeed true that gross fibre arrangement in the ventricular septum is such that the midsegment is the area in which the greatest regularity can be expected in normal hearts.[43] Sections from this site (our block 4), however, showed disarray as the leading feature in one of our five hearts, while minor deviations were present in the other four.

It is our firm belief that most of the current controversies concerning myocardial disarray relate to differences in opinion of what is normal and what is abnormal in myocardial histology. What, for instance, is the evidence that a parallel alignment of cells should be considered as normal? We thought it almost common knowledge that muscle cells in the myocardium are not aligned in parallel.[45] Indeed, a popular textbook of histology says of the myocardium that "the fibres are not simple cylindrical units but they bifurcate and connect with adjacent fibres to form a complex three dimensional network".[46]

As long ago as 1694 van Leeuwenhoek,[47] in his correspondence with the Royal Society in London, beautifully portrayed different fascicle arrangements and branching cells in the myocardium of the heart of the duck (Fig. 7). According to criteria set today for normality, van Leeuwenhoek's drawings display minor deviations of normality as well as disorganisation. It could, of course, be argued that disorganisation is "normal" for ducks and that a similar architecture in man is anomalous. Some investigators have pointed out that the embryonic heart of various animal species contains myocardial disarray to a great extent,[13 48 49] and the group from Bethesda has shown disorganisation as the histological hallmark in both canine and feline hypertrophic cardiomyopathy.[50 51]

Be that as it may, other investigators concerned only with the normal human heart have found replicas of van Leeuwenhoek's observations at many places in the myocardium. Indeed, our present study points out that a parallel alignment of myocardial fibres cannot be promoted as the paradigm of normality. The intricate architecture of mostly obliquely oriented layers of fibres must dictate that different orientations of sections produce histological patterns, some of which by necessity produce characteristics of "disorganisation".

The above discussion should not be construed as suggesting that myocardial disarray is not a feature of hypertrophic cardiomyopathy. What we emphasise is that disorganisation—as a microscopical feature—is by itself not necessarily an indication of an *ab*normality. We do not want to deny that myocardial disarray may be more extensively present in hearts with hypertrophic cardiomyopathy. Both clinician and pathologist, however, should know that a change in orientation of one and the same block of tissues may actually turn "normality" into "disarray"!

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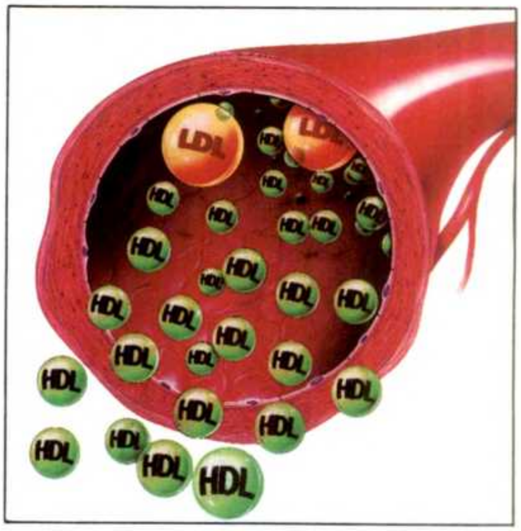

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Effects of histamine type 2 receptor stimulation on myocardial function in normal subjects

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SUMMARY Myocardial histamine $(H)_2$ receptor stimulation has been studied in six normal men. Since histamine is a potent vasodilator, the haemodynamic effects of histamine infusion were compared with those of nitroprusside at equihypotensive doses, to identify changes in myocardial contractility attributable to vasodilatation.

After H_1 receptor blockade with mepyramine, subjects received, in single blind crossover fashion, either histamine alone and with the H_2 receptor antagonist cimetidine, or nitroprusside alone and with cimetidine. Echocardiographic left ventricular dimensions, plasma catecholamines, blood pressure, and heart rate were measured. The rise in catecholamines suggested similar baroreflex activation by both histamine and nitroprusside. Echo ejection phase indices did not alter significantly after nitroprusside, but histamine caused an increase in percentage fractional shortening from 38·2±4·1 to 53·5±3–6% and in mean fibre shortening velocity from 1·31±0·19 to 1·99±0·22 cm/s. These changes were both greatly reduced by cimetidine and suggest that H_2 receptor stimulation in man causes a direct positive inotropic response.

Histamine has multiple sites of action within the cardiovascular system, subserved by two receptor populations, types H_1 and H_2.[1] Human myocardium[2] and arterial wall[3] are both thought to contain H_1 and H_2 receptors. Histamine infusion causes flushing, vasodilatation, and increased cardiac output in man.[4] It is not clear, however, whether this increase in cardiac output is merely secondary to the fall in systemic vascular resistance and increase in heart rate, or the result of a direct myocardial positive inotropic effect of histamine.

Isolated mammalian heart studies have shown four major effects of histamine[5–7] including a positive chronotropic effect, a negative dromotropic effect (decreased atrioventricular conduction), a positive inotropic effect, and increased cardiac automaticity.

The receptor types mediating these effects are species specific[5–7] but, in several preparations, H_1 receptor stimulation gives a positive chronotropic and negative dromotropic effect and an increase in cardiac automaticity. Recent in vitro studies in isolated *human* fetal heart have also shown an H_2 receptor mediated positive inotropic response.[2] No in vivo studies in man have previously been performed and, before the availability of cimetidine, human study in vivo was greatly restricted by the absence of a safe H_2 receptor antagonist.

It is now known that both H_1 and H_2 receptors mediate vasodilatation in man[8] and, though the widespread use of cimetidine (a specific H_2 receptor antagonist) for the treatment of peptic ulceration has been regarded as being without significant cardiovascular risk, isolated case reports of bradycardia, heart block, and hypotension have been reported.[9–12]

No obvious physiological or pathological role for myocardial histamine receptors has emerged, though they may be important in mediating the cardiovascular sequelae in anaphylaxis.[13]

We have, therefore, studied, by non-invasive means, the effects of direct myocardial H_1 receptor stimulation in man.

Subjects and methods

Six male volunteers, weighing 74·0±4·2 (±1 SD) kg and aged 29 to 34 years, were studied. All were nor-

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motensive, free from cardiovascular disease, and had normal resting electrocardiograms and M-mode echocardiograms. (Subjects with a history of atopy, bronchospasm, dyspepsia, or urticaria were specifically excluded.)

Written informed consent was obtained and the procedure was approved by the Research Ethics Committee of the Royal Postgraduate Medical School, London. These studies were performed under basal conditions in a warm, well lit, clinical laboratory. Each subject was studied twice (once with histamine and once with nitroprusside) and the studies were performed at least 48 hours apart, but at approximately the same time of day. Subjects were fasted for four hours, were all non-smokers, and took no caffeine-containing beverages or medications of any kind in the week preceding study.

A "19" gauge butterfly needle (Abbott) was inserted into a peripheral arm vein for collection of blood for catecholamine estimation, and was primed with heparinised saline. A 5 in polythene intravenous cannula (Medicath.) was inserted into an antecubital vein on the opposite arm for drug administration by means of a variable delivery rate infusion pump (Braun). Subjects were then instructed to lie in a 50° left anterior oblique position, which was individually optimised for M-mode echocardiographic recording (Cambridge and Irex Instruments Ltd) of left ventricular cavity dimensions. This position was then unchanged for the remainder of the study. A simultaneous indirect right carotid artery waveform was also recorded, using a pressure sensitive device held against the neck. All recordings were taken during quiet, normal respiration. Heart rate was displayed and the electrocardiogram visualised on a cardiac monitor (Hewlett Packard). Systemic blood pressure was recorded in duplicate from the right arm, using an automatic ultrasonic recorder (Arteriosonde Roche 1217).

Subjects received, single blind, four consecutive 20 minute drug infusions (Fig. 1). Blood pressure and heart rate were recorded every minute and, in addition, plasma catecholamines, echocardiographic left ventricular cavity dimensions, and carotid arterial waveform were recorded, in that order, in the final five minutes of each infusion: (1) saline 0·9% at 1 ml/minute; (2) mepyramine (a specific H_1 receptor antagonist), 0·05 mg/kg/per min to a mean total dose of 74·0 mg; (3) in randomised, crossover fashion, either (a) histamine acid phosphate or (b) sodium nitroprusside.

The infusion rates for the histamine and nitroprusside were adjusted over the first nine minutes to cause a stable fall in diastolic blood pressure of 15 mmHg, compared with post-mepyramine values. Histamine infusions were started at 1·0 μg/kg per min and increased as necessary every three minutes by 0·25 μg/kg per min (mean rate required 1·5±0·10 μg/kg per min). Nitroprusside infusions were started at 0·2 μg/kg per min and increased as necessary every three minutes by 0·2 μg/kg per min (mean rate required 0·6±0·16 μg/kg per min). Both histamine and nitroprusside infusions were light shielded.

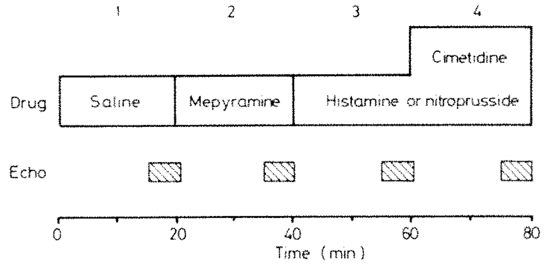

Fig. 1 *Study procedure.*

With either histamine or nitroprusside continuing for a further 20 minutes, cimetidine (a specific H_1 receptor antagonist) was given in a bolus of 100 mg over three minutes via the butterfly needle, followed by an infusion of 0·2 mg/kg per min (mean total dose 396 mg). The initial bolus was given to achieve rapid blood levels of ≥ 1 μg/ml, a concentration known to inhibit H_2 receptor mediated gastric acid release by at least 50%.[14]

All blood samples were of 10 ml volume, taken into chilled glass lithium heparin tubes, spun immediately at 4°C, separated, and the plasma stored at −20°C for assay within two weeks. Plasma noradrenaline and adrenaline were determined by the radioenzymatic catechol-o-methyl transferase method of Da Prada and Zürcher.[15] The coefficients of variation within and between assays were 2·9 and 5·3%, respectively, and the sensitivity of the assay for both noradrenaline and adrenaline was 3 pg.

All M-mode echocardiographic recordings were performed through the same interspace on each individual and by the same investigator, the transducer placement being marked indelibly on the chest wall at the first study. Standard recordings of the left ventricular cavity just below the mitral valve were obtained over six cardiac cycles,[16] using a 2·5 MHz unfocused transducer and a paper speed of 5 cm/s. Left ventricular dimensions were measured between the endocardial surfaces of the posterior wall and the left side of the ventricular septum using the "leading edge" convention. Only subjects in whom septal and posterior wall endocardial echoes could be defined throughout the cardiac cycle were included in the study. The left ventricular end-diastolic dimension (EDD) was measured coincident with the peak of the R wave of a simultaneously recorded electrocardiogram. The left ventricular end-systolic dimension (ESD) was defined as the smallest distance between septal and posterior wall endocardial surfaces during systole. Left ventricular ejection time (ET) was measured from the initial rapid upstroke of the carotid arterial pulse to the incisura of the dicrotic notch. Fractional shortening (FS) was calculated as (EDD-ESD)/EDD%. The mean normalised velocity of left ventricular fibre shortening was calculated as (EDD-ESD)/(EDD×ET).

The data of each individual were measured over six cardiac cycles and averaged. All echo recordings were read "blind" by two investigators (JW and HJD) and their measurements were averaged in the event of disparity. Records were measured to the nearest 1 mm. Final data presented were the mean of six subjects±1 standard deviation from the mean.

Statistical analysis was performed by least squares analysis of variance and, where appropriate, by paired "t" tests.

Results

Except where otherwise stated, statistical comparisons refer to differences between data derived from parallel steps in the histamine and nitroprusside studies. In Table 1 the effects of histamine and nitroprusside infusions have been compared with the effects of mepyramine to allow identification of a specific H_2 effect of the histamine infusion. There was, however, no significant difference in any variable between the saline and mepyramine periods. Three subjects experienced some nausea during the mepyramine infusion with associated pallor and a reduction in heart rate of 79 beats a minute. Diastolic blood pressure also rose 3 to 5 mmHg. Thereafter haemodynamic observations were stable.

Histamine, in addition to its haemodynamic effects, caused distinct flushing of the face and trunk, conjunctival suffusion, and mild throbbing headache. All subjects reported an awareness of forceful heartbeat. These effects were all rapidly and totally reversed by cimetidine. Mild facial flushing was observed in two subjects during nitroprusside infusion and this was not reversed by cimetidine.

BLOOD PRESSURE

A stable fall in diastolic blood pressure of 17 mmHg was achieved with nitroprusside and of 15 mmHg with histamine (Table 1). Systolic blood pressure fell 10 and 3 mmHg, respectively. The absolute values of blood pressure after these two drugs were not significantly different. Concurrent administration of cimetidine reversed the hypotension caused by histamine, but not that caused by nitroprusside.

HEART RATE

Histamine caused a rise in heart rate of 12 beats a minute and nitroprusside of seven beats a minute compared with post-mepyramine heart rates (NS). Cimetidine did not significantly inhibit the tachycardia induced by either vasodilator (Table 1).

CATECHOLAMINES

Plasma noradrenaline rose from 1·24±0·47 to 1·77±0·24 nmol/l (0·21±0·08 to 0·30±0·04 ng/ml) during histamine ($p<0·05$) and from 1·30±0·35 to 1·83±0·41 nmol/l (0·22±0·06 to 0·31±0·07 ng/ml) during nitroprusside ($p<0·05$).

Plasma adrenaline rose from 0·23±0·033 to 0·29±0·06 nmol/l (0·042±0·006 to 0·053±0·012 ng/ml) during histamine ($p>0·05$), and from 0·23±0·033 to 0·31±0·06 nmol/l (0·042±0·006 to 0·056±0·011 ng/ml) during nitroprusside ($p>0·05$).

Basal levels of both noradrenaline and adrenaline fell within our laboratory normal range for supine rest. Catecholamine levels at peak histamine and peak nitroprusside infusions were not significantly different.

LEFT VENTRICULAR CAVITY DIMENSIONS

End-systolic and end-diastolic dimensions are shown in Fig. 2. End-diastolic dimensions were not significantly altered by any drug intervention. During histamine it was 5·1±0·3 cm, and during nitroprusside it was 4·8±0·3 cm (NS). There was a tendency in

Table 1 *Blood pressure and heart rate changes (± standard deviation) in histamine and nitroprusside studies*

Drug	*Blood pressure (mmHg)*		*Heart rate (beats/min)*	
	Histamine study	*Nitroprusside study*	*Histamine study*	*Nitroprusside study*
Saline	116/73±10/9	116/73±11/3	75±10	73±9
Mepyramine	117/76±9/7	120/80±9/6	68±6	68±11
H/NP infusion	114/61*±11/6	110/63†±9/3	80±14	75±7
H/NP infusion+cimetidine	118/75‡±11/8	114/66±8/8	76±9	75±8

H, histamine; NP, nitroprusside; *$p<0·05$ compared to mepyramine; †$p<0·01$ compared to mepyramine; ‡$p<0·05$ compared to histamine.
Note: Nitroprusside caused a fall in diastolic blood pressure of 17 mmHg and histamine of 15 mmHg compared with mepyramine, but absolute values of blood pressure during histamine and nitroprusside infusions were not significantly different.

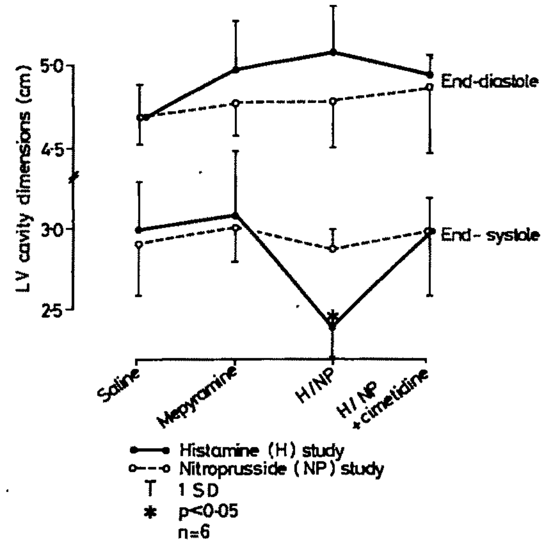

Fig. 2 *Effect of histamine and nitroprusside on left ventricular short axis cavity dimensions.*

both studies for the end-diastolic dimension to increase as a function of time.

End-systolic dimension, however, was reduced from 3·1±0·4 cm after mepyramine to 2·4±0·2 cm during histamine ($p<0·05$). During the nitroprusside infusion no comparable fall in end-systolic dimension was seen at an equihypotensive dose, the dimension remaining unchanged at 2·9±0·1 cm ($p<0·05$ compared with end-systolic dimension during histamine).

In the histamine study, end-systolic dimension returned to 3·0±0·2 cm after concomitant administration of cimetidine ($p<0·05$ compared with end-systolic dimension during histamine alone).

ECHO EJECTION PHASE INDICES

(a) *Fractional shortening*

Histamine infusion caused a pronounced increase in fractional shortening compared with nitroprusside at equihypotensive doses (see Fig. 3a). At peak histamine infusion, fractional shortening was 53·5±3·6% whereas at peak nitroprusside infusion it was only 39·2±5·4% ($p<0·05$). Cimetidine administration during the histamine infusion caused a reduction in fractional shortening to 40·3±3·1% ($p<0·05$ compared with fractional shortening during histamine alone) but no significant change when added during the nitroprusside infusion.

(b) *Fibre shortening velocity*

Fibre shortening velocity increased from 1·31±0·19 to 1·99±0·22 cm/s during histamine ($p<0·05$)—see Fig. 3b. Nitroprusside caused a smaller rise, from 1·23±0·11 to 1·49±0·22 cm/s ($p<0·05$). Both absolute and indexed values at peak histamine, however, were significantly greater than those during nitro-

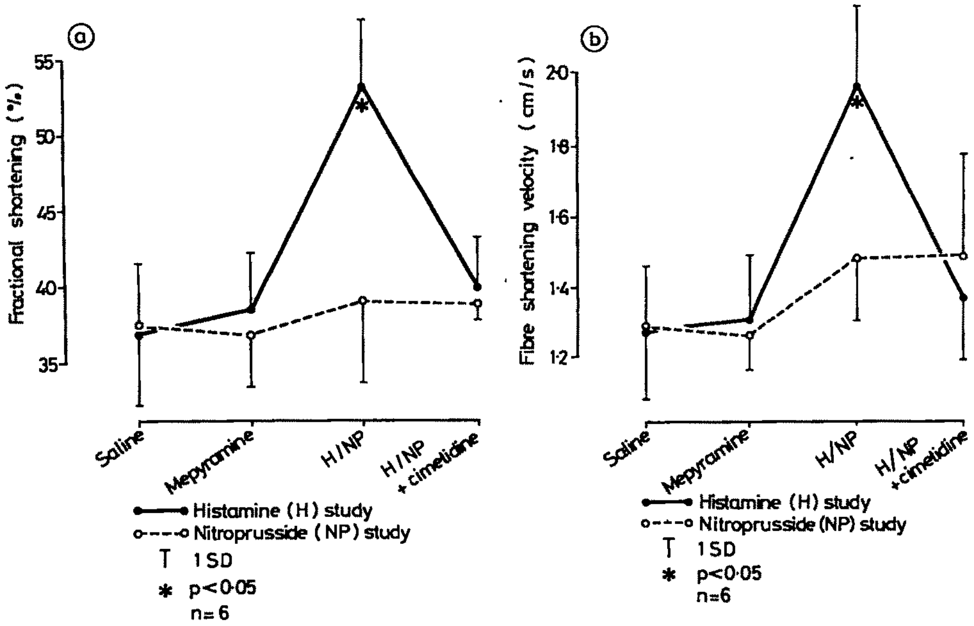

Fig. 3 *Effect of histamine and nitroprusside on echocardiographic ejection phase indices of left ventricular performance. (a) % fractional shortening, (b) fibre shortening rate.*

Table 2 *Left ventricular ejection times (observed and indexed) during histamine and nitroprusside studies*

Drug	*Observed LVET (ms)*		*Indexed LVET (ms) (observed LVET+1·7×HR)*	
	Histamine study	*Nitroprusside study*	*Histamine study*	*Nitroprusside study*
Saline	288±16	286±16	416±4	410±14
Mepyramine	292±16	299±8	407±6	416±6
H/NP infusion	269±30*	263±24*	405±12	391±20*
H/NP infusion+cimetidine	292±24†*	260±14	423±6†*	390±18

H, histamine; NP, nitroprusside; LVET, left ventricular ejection time.
Note: There were no significant differences between LVET during the H and NP infusions. Note, however, that both H and NP infusions caused LVET to shorten compared with LVET after mepyramine (*$p<0·05$), but that cimetidine reversed only that shortening in LVET caused by histamine (†*$p<0·05$).

prusside infusion (all $p<0·05$). Cimetidine reversed the histamine-induced increase in fibre shortening velocity, but had no effect when given with nitroprusside.

LEFT VENTRICULAR EJECTION TIME

Absolute and indexed ejection times are shown in Table 2. Both histamine and nitroprusside caused left ventricular ejection time to shorten compared with ejection times after mepyramine, but cimetidine reversed only the shortening in ejection time caused by histamine ($p<0·05$ compared with the ejection time during histamine alone).

Discussion

This study has confirmed the presence of myocardial H_2 receptors in normal subjects, and shown that stimulation of these receptors gives a positive inotropic response. The study was designed in such a way that changes in myocardial contractility directly and reflexly attributable to vasodilatation could be identified. This was achieved by comparing the haemodynamic effects of histamine with those of nitroprusside. Both are potent, short acting vasodilators, but nitroprusside is known to have no direct myocardial effects.[17] By infusing the same subjects with both drugs at concentrations which gave a similar fall in diastolic blood pressure, we assumed that comparable decreases in peripheral vascular resistance had been achieved. By measuring plasma noradrenaline, an index of sympathetic function,[18 19] baroreflex activation caused by both vasodilators was also compared. The similar rise in plasma noradrenaline during histamine and nitroprusside infusions suggested an equivalent degree of baroreflex activation in both studies. Though histamine and nitroprusside are both vasodilators,[17 20] their relative potencies are unknown. Left ventricular end-diastolic dimension, however, which reflects preload,[21] was not significantly altered by either drug, so we feel it was unlikely that the improvements in left ventricular performance during histamine H_2 receptor stimulation could be solely ascribed to differences in their venodilator properties. Plasma adrenaline was measured, since the positive inotropic effect of histamine might have been mediated by release of catecholamines from the adrenal medulla. In the presence of mepyramine, an H_1 receptor antagonist, however, plasma adrenaline levels were similar and not significantly raised during either histamine or nitroprusside infusion. Therefore, if histamine does liberate adrenal medullary catecholamines directly, the response is H_1 receptor mediated in man and does not contribute to the positive inotropic effect of histamine H_2 receptor stimulation seen in this study.

Thus, an improvement in left ventricular performance was observed during histamine H_2 receptor stimulation, which appeared not to have been attributable to the direct or reflex effects of vasodilatation. Moreover, this effect was almost completely reversed by concomitant administration of cimetidine, an H_2 receptor antagonist which in the regimen used in this study has no apparent intrinsic haemodynamic effects.[14] (Unpublished studies from our own laboratory have also failed to show any haemodynamic effects following acute intravenous administration of cimetidine in normal subjects.)

There was no increase in atrioventricular conduction during histamine infusion in the presence of mepyramine, nor any evidence of bronchospasm, suggesting that significant H_1 blockade had been achieved. There was, however, a small increase in heart rate but, since this was of the same order of magnitude as that observed during the nitroprusside infusion, we feel that it was likely to be a reflex change secondary to vasodilatation and not due to H_1 receptor stimulation. The incomplete reversal by cimetidine of the increase in heart rate during histamine infusion by cimetidine gives rise to the alternative possibility that it was, at least partially, H_2 receptor mediated.

Histamine has other cardiovascular effects that were not measured or controlled in this study, that is effects on coronary vascular resistance, respiratory influences, direct cerebral effects on the vasomotor centre, and changes in vascular permeability.[22] While these changes may have accounted for some of the increase in myocardial contractility seen, it is unlikely that their contribution was great. Though cimetidine may cross the blood-brain barrier in man after chronic dosing,[23] the reversal of the positive inotropic effect was very rapid after cimetidine administration. A centrally mediated effect, therefore, seems less likely, but cannot be ruled out. The effects of vascular permeability could not be quantified and there are no human data. Animal studies, however, suggest that these permeability effects are predominantly H_1 receptor mediated and therefore not contributory to the changes seen in this study.[24]

The echocardiographic ejection phase indices used have been shown to correlate well with measures of myocardial contractility determined angiographically.[25] Since serial measurements of left ventricular cavity dimensions in the same subject at rest can vary, even under ideal conditions, by ±3·5 mm (approximately 10% of the end-systolic dimension),[26] dimension changes need to be considerably larger than this before they can be confidently ascribed to a drug effect.[27] In this study, histamine caused a reduction of end-systolic dimension of 7 mm (−22%).

This was an acute study and there was no measure of the duration of the positive inotropic response. Histamine analogues with specific H_2 receptor agonist properties[28 29] have recently been developed which may enable chronic studies on myocardial H_2 receptor stimulation to be made. It will be important to determine whether specific H_2 receptor agonists cause a sustained positive inotropic effect and reduction of peripheral vascular resistance in man without undue tachycardia or other unwanted systemic effects: the therapeutic implications of this remain speculative but could include inotropic support in heart failure.

We thank the manufacturers for the loan of Cambridge and Irex echocardiographic equipment for this study.

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The electrocardiogram in apparently healthy men and the risk of sudden death

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SUMMARY The purpose of this study was to determine whether electrocardiographic abnormalities detected on a routine examination in men without clinical evidence of heart disease predicted sudden death in the absence of pre-existing clinical manifestations of heart disease. The Manitoba study consists of a cohort of 3983 men with a mean age at entry of 30·8 years who have been followed with regular examinations including electrocardiograms since 1948. During the 30 year observation period, 70 cases of sudden death have occurred in men without previous clinical manifestations of heart disease. The prevalence of electrocardiographic abnormalities before sudden death was 71·4% (50/70). The frequency of abnormalities was 31·4% (22) major ST segment and T wave abnormalities, 15·7% (11) ventricular extrasystoles, 12·9% (nine) left ventricular hypertrophy (voltage criteria), 7·1% (five) complete left bundle-branch block, and 5·7% (four) pronounced left axis deviation. When these electrocardiographic findings in men without clinical manifestations of heart disease were related prospectively to incidence of sudden death each one except pronounced left axis deviation was a significant predictor of sudden death. Two of the variables were examined in more detail. Increased severity of primary T wave abnormalities and the association of ST segment and T wave abnormalities with increased QRS voltage further increased sudden death risk. The combination of ventricular extrasystoles with either ST-T abnormalities or left ventricular hypertrophy much increased the risk of sudden death. Thus these data indicate that electrocardiographic abnormalities detected on routine examination in men without clinical evidence of heart disease are significantly related to the occurrence of sudden death.

Sudden death has become recognised as a major challenge in contemporary cardiology with the realisation that it is the most frequent mode of death in ischaemic heart disease.[1–3] Investigations of this problem have mainly centred on sudden death in patients with known cardiac disease and there are comparatively few data available in men without previous clinical evidence of ischaemic heart disease. Because in this circumstance it is their first and usually their last clinical manifestation of heart disease, it is especially important to identify high risk groups for sudden death. The electrocardiogram which is in widespread use primarily as a diagnostic tool is less often used in prognosis especially as it relates to apparently healthy subjects. Yet the electrocardiogram is used in the screening of healthy individuals in many settings and represents a simple non-invasive method of cardiac assessment that may be of value in risk stratification. The purpose of this investigation was to examine the hypothesis that the "routine" electrocardiogram in apparently healthy men is predictive of sudden death.

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Subjects and methods

The details of this study have been reported previously.[4 5] In summary, the cohort consists of 3983 men, who during the second world war were either pilots or pilots in training in the Royal Canadian Air Force, or pilots licensed by the Department of Transport and who at the time had a routine electrocardiogram in addition to the regular medical examination. After release from the service, some continued to fly but the majority found different occupations and are in all strata of society.

For each subject, the examination closest to 30 June 1948 (date population was defined) was selected as the entry examination. The age distribution at entry was as follows: 318 men were aged 15 to

24 years, 1479 aged 25 to 29, 1258 aged 30 to 34, 539 aged 35 to 39, 205 aged 40 to 44, 153 aged 45 to 54, and 31 aged 55 to 64 years. Earlier medical information and examinations provided evidence that they were without clinical manifestations of ischaemic heart disease at entry. Since then, they have been followed by annual letters with medical examinations and electrocardiograms at intervals of at first five and later three years. The observation period was defined from 1 July 1948 until 30 June 1978, an average follow-up of 30 years. Annual contact has been lost with only two persons.

DEFINITIONS AND CASE DETECTIONS

Cases were selected if they had (1) electrocardiographic abnormality detected during a routine examination, and (2) no clinical evidence of ischaemic or valvular heart disease on either that examination or the previous ones since entry. Thus, men with myocardial infarction, angina pectoris, or coronary insufficiency before the detection of the electrocardiographic abnormalities were excluded. The diagnostic criteria used for these manifestations of ischaemic heart disease were outlined previously.[5] For myocardial infarction, this included detection of new abnormal ($\geqslant 0{\cdot}03$ s) Q wave even in the absence of clinical symptoms—silent myocardial infarction. Thus the cases selected had no electrocardiographic—Q wave evidence of myocardial infarction. The definition of sudden death was that of the WHO, namely natural death occurring immediately or within an estimated period of 24 hours after the onset of acute objective or subjective symptoms of ischaemic heart disease.[6] During the observation period there were 70 sudden deaths with an age distribution at death as follows: less than 40 years, three men (4%); 40 to 49 years, 13 men (19%); 50 to 59 years, 30 men (43%); 60 to 69 years, 20 men (29%); and 70 to 74 years, four men (6%).

Necropsies were done in 25 of the 70 cases. Despite the absence of clinical symptoms, 96% (24/25) of cases had severe coronary atherosclerosis as evidenced by lesions reducing coronary artery lumen of greater than 75% and the other case had moderate—50 to less than 75% luminal narrowing by coronary atherosclerosis.

Left axis deviation

The mean frontal plane QRS vector was determined from the limb leads using a hexaxial reference system.[7] The vector was calculated to the nearest 15° because, as pointed out by others,[8] this is a reasonable limit of precision for the standard electrocardiogram.

The definition of left axis deviation was (1) a mean frontal plane QRS vector of $-45°$ to $-90°$; (2) a QRS duration of 110 ms or less, and (3) the absence of Wolff-Parkinson-White syndrome, complete left bundle-branch block, and complete right bundle-branch block.

During the 30 year observation period 286 men fulfilled the clinical and electrocardiographic criteria. The age distribution at detection of the electrocardiographic abnormality was 20 to 29 years, 24 men; 30 to 39 years, 43 men; 40 to 49 years, 71 men; 50 to 59 years, 97 men; 60 to 69 years, 42 men; 70 to 79 years, eight men; 80 years, one man.

Bundle-branch block

The criteria for the diagnosis of right and left bundle-branch block were outlined by the New York Heart Association[9] and the Minnesota code.[10] The criteria include QRS duration of 0·12 s or greater and for right bundle-branch block an r SR, q R, or a tall R wave in V1 and for left bundle-branch block QRS notching and terminal conduction delays in limb (I, aVL) or precordial (V5–6) leads. During the observation period 33 cases of complete left bundle-branch block were detected. The age distribution was 30 to 39 years, three men; 40 to 49 years, seven men; 50 to 59 years, 10 men; 60 to 69 years, 11 men; 70 and over years, two men. For right bundle-branch block, 65 cases were detected and had an age distribution as follows: younger than 20 years, two; 20 to 29 years, 12; 30 to 39 years, eight; 40 to 49 years, 13; 50 to 59 years, 20; 60 to 69 years, eight; 70 and over, two men.

Ventricular extrasystoles

The criteria for identification of ventricular extrasystoles were (1) different QRS morphology from the dominant rhythm, (2) QRS duration of 0·12 s or greater, (3) premature in occurrence, (4) no preceding premature p wave.[11] The age distribution of the 428 cases detected was as follows: younger than 20 years, one; 20 to 29 years, 20; 30 to 39 years, 55; 40 to 49 years, 89; 50 to 59 years, 177; 60 to 69 years, 76; 70 years and older, 10 men.

Left ventricular hypertrophy

Voltage criteria for left ventricular hypertrophy were the essential criteria for definition of this entity. One of three criteria had to be satisfied, either R wave in V5 or V6 greater than 26 mV, R wave in aVL greater than 11 mV, or sum of S in V1 and R in V5 or V6 greater than 35 mV.[10 12] Cases were also analysed according to presence or absence of associated ST and T findings. The age distribution of the 254 cases of increased QRS voltage were as follows: 20 to 29 years, one man; 30 to 39 years, 48 men; 40 to 49 years, 81 men; 50 to 59 years, 79 men; 60 to 69 years, 40 men; 70 years and older, five men.

ST segment and T wave abnormalities

The description of major ST segment and T wave deviations was that outlined in the Minnesota code.[10] They are coded only in the absence of bundle-branch block, left ventricular hypertrophy, and Wolff-Parkinson-White conduction. ST segment abnormalities were defined as equivalent to Minnesota codes 1 to 3, that is either ST-J depression 1 mV or greater with the ST segment horizontal or downward sloping, or ST-J depression 0·5 to 1·0 mV with ST segment horizontal or downward sloping, or no ST-J depression 0·5 mV but ST segment downward sloping so that it or T wave nadir is 0·5 mV or greater below the p–r baseline. The age distribution of the 253 cases of ST segment abnormality was for ages 20 to 29 years, one man; 30 to 39 years, nine men; 40 to 49 years, 29 men; 50 to 59 years, 126 men; 60 to 69 years, 71 men; 70 years and older 17 men.

T wave abnormalities were coded as present if the T wave was isoelectric or inverted (Minnesota code 1 to 3) in leads I or II or V2 or V3 or any two of V3 to V6. The age distribution of the 440 cases of T wave abnormality was ages 20 to 29 years, eight men; 30 to 39 years, 27 men; 40 to 49 years, 73 men; 50 to 59 years, 217 men; 60 to 69 years, 92 men; 70 years and older, 23 men. The frequency association of ST segment and T wave abnormalities and the clinical thinking that considers them together lead to the combination of both to form one group.

Major ST and T wave changes were subject to data analysis, but T waves were also coded for the presence of *minor* T abnormality, namely reduction in T wave amplitude (Minnesota code T wave code 4) in leads I, II, V2, and V3 or any two of leads V3 to V6.

DATA ANALYSIS

To account for age and varying lengths of follow-up, after the development of electrocardiographic abnormalities, the person-year exposure to each abnormality within age groups was calculated. The age specific rates of sudden death per 1000 person years of exposure were calculated from onset of each electrocardiographic abnormality and for the entire cohort from the first 12 lead electrocardiogram. The relative risk, namely the sudden death incidence in those with the electrocardiographic abnormality divided by the incidence in those without the abnormality, was also calculated. Hypothesis testing used the χ^2 approach. The null hypothesis was rejected if the probability of a type 1 error was less than 5%.

Results

PREVALENCE OF ELECTROCARDIOGRAPHIC ABNORMALITIES IN SUDDEN DEATH CASES

The prevalence of abnormalities on the routine electrocardiograms in men without apparent heart disease who died suddenly is shown in Table 1. The majority or 71·4% (50/70) of cases had previous electrocardiographic abnormalities. The most frequent findings was ST segment or T wave abnormalities occurring in 50% of cases though in only 31·4% was it classifiable as a major abnormality. Ventricular extrasystoles were the next most frequent finding, then left ventricular hypertrophy, left bundle-branch block, and pronounced left axis deviation. There were no cases with pre-existing complete right bundle-branch block.

ELECTROCARDIOGRAPHIC VARIABLES AND SUDDEN DEATH PREDICTION

The age adjusted sudden death incidence for those with and without each of the electrocardiographic abnormalities is shown in Fig. 1. The highest sudden

Table 1 *Prevalence of electrocardiographic abnormalities in men without apparent heart disease who later died suddenly*

Abnormality	%	*No.*
ST segment—T wave	50	35
Major	31·4	22
Minor	18·6	13
Ventricular extrasystoles	15·7	11
Left ventricular hypertrophy	12·9	9
QRS voltage criteria and ST segment and T abnormalities	10·0	7
QRS voltage criteria only	2·9	2
Complete left bundle-branch block	7·1	5
Pronounced left axis deviation	5·7	4
PR interval greater than 0·22 s	1·4	1
Complete right bundle-branch block	0·0	0

These abnormalities coexisted in some patients so that 71·4% (50/70) had one of the above abnormalities and 23·6% (20/70) had none.

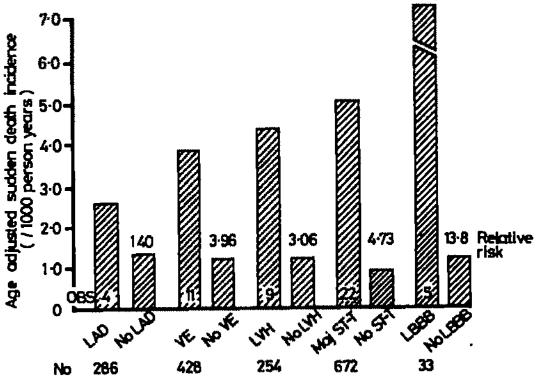

Fig. 1 *The age adjusted sudden death incidence for those with and without each of the following electrocardiographic abnormalities: pronounced left axis deviation (LAD), ventricular extrasystoles (VE), left ventricular hypertrophy (LVH), major ST segment or T wave abnormalities (Maj ST-T), and complete left bundle-branch block (LBBB). The number of sudden death cases observed (OBS) in each subgroup with each electrocardiographic abnormality and the relative risk for sudden death are also shown.*

death incidence rate was for complete left bundle-branch block which was significantly (p<0·05) greater than the absence of left bundle-branch block. The relative risk for sudden death was 13·8. Major ST segment and T wave abnormalities, increased R wave voltage, and ventricular extrasystoles were all significantly (p<0·05) associated with sudden death with relative risks from 4·8 to 3·7. Pronounced left axis deviation was not significantly associated with sudden death.

Two of the variables, namely left ventricular hypertrophy and ST segment and T wave changes, could be examined in more detail. For left ventricular hypertrophy, the highest incidence of sudden death was in men in whom increased QRS voltage and ST segment and T wave abnormalities occurred together (Table 2). The next highest incidence of sudden death was in those with increased QRS voltage and no associated ST segment or T wave abnormalities subsequently. To examine the relation between sudden death and the severity and location of T wave abnormalities the small number of cases in each subset made the analysis of proportions preferable. Risk of sudden death increased with increasing severity of T wave abnormality. It was greater with abnormalities in leads V4 to V6, then V2 and V3, then lead II, and lastly lead I (Fig. 2). Combinations of electrocardiographic abnormalities, where relevant, showed a pronounced increase in sudden death risk (Fig. 3). Further subdivision of these combinations was not possible because of the small numbers in many subsets.

Discussion

This study has demonstrated that certain abnor-

Table 2 *Age adjusted incidence of sudden death for left ventricular hypertrophy according to presence or absence of associated ST segment or T wave abnormalities*

Criteria	*Cases with ECG finding*	*Cases of sudden death*	*Age adjusted sudden death rate per 1000 person year*
QRS voltage with ST-T findings at first occurrence voltage evidence	51	3	13·47
QRS voltage and ST-T findings at any time	89	4	8·33
QRS voltage with no ST-T findings at first occurrence voltage evidence	203	5	2·78
QRS voltage with no ST-T findings at any time	215	5	2·68
QRS voltage alone (regardless ST-T findings)	254	9	4·79

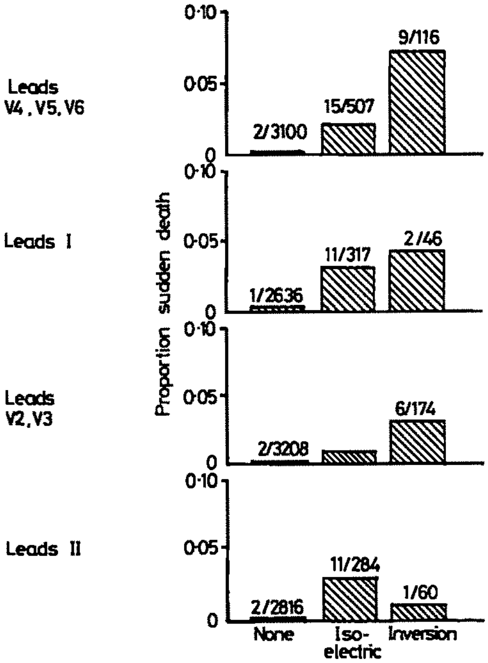

Fig. 2 *The proportion of sudden death within 10 years of the occurrence of T wave abnormalities defined by the presence and severity of the T wave findings and the lead(s) in which they occur.*

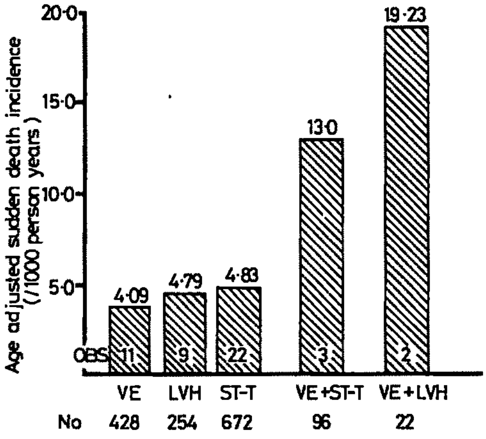

Fig. 3 *The age adjusted sudden death incidence for those with combinations of electrocardiographic abnormalities, namely ventricular extrasystoles (VE) plus left ventricular hypertrophy (LVH) or ST segment/T wave abnormalities (ST-T). For comparison, the incidence of sudden death is again shown when the abnormalities occur alone.*

malities detected on a resting electrocardiogram in apparently healthy men are associated with a significantly increased risk of sudden death. Left bundle-branch block, left ventricular hypertrophy, major ST segment and T wave abnormalities, and ventricular extrasystoles occurring individually and combinations of the last three are predictors of sudden death. There are, however, several major caveats with regards to the extrapolation of these results. Firstly, though there is concern that none of the prospective studies of cardiovascular disease epidemiology is representative of the general population[13] the selective nature of this cohort must be remembered. A strength of this study, however, is the relatively young age at entry and the repeated examinations which permit identification of onset of new abnormalities and assurance that there was no heart disease at entry. Secondly, the incidence rate of sudden death in apparently healthy individuals is low.[2 14] Though the numbers of cases of sudden death in men without previous heart disease in our study are comparable with others,[14] nevertheless the small number of cases overall and especially in groups with combinations of abnormalities suggest that conclusions must be drawn cautiously. Thirdly, the difficulties of longitudinal data analysis become even more complex when electrocardiographic variables are analysed. We chose to classify individuals as abnormal from the first detection of the electrocardiographic abnormality regardless of the findings on subsequent tracings. This was done because some abnormalities such as bundle-branch block are relatively permanent once they occur and others such as ventricular extrasystoles are transient, in part because of the short duration of the resting electrocardiogram. Another reason for this approach is that the occurrence of cardiovascular disease or death in the period between electrocardiographic examinations is a confounding factor in classifications of subsequent presence or absence of electrocardiographic abnormalities. Thus our data must be evaluated within this context. Our classification of electrocardiographic abnormalities is equivalent to the Minnesota code criteria with the following exceptions. Left axis deviation starts from −45° rather than from −30°. Our criteria for ventricular extrasystoles and bundle-branch block are specified in more detail and for left ventricular hypertrophy we do not use R amplitude in limb leads except aVL, but use an additional precordial QRS criterion. For data analysis, cases with Q wave abnormalities consistent with the clinical diagnosis of "silent" myocardial infarction were the only ones excluded because they can be considered to have ischaemic heart disease already and thus have an increased risk of sudden death. Their exclusion must be remembered for comparison with other studies. Another issue is the ever present problem of whether the "apparently healthy individual" truly represents an individual without heart disease. Clinically occult ischaemic heart disease may have been the underlying causative factor for the electrocardiographic abnormalities and thus responsible for the prognosis. From a pragmatic standpoint, however, the electrocardiogram might even be viewed as a test for clinically occult disease and its prognostic ability assessed from that perspective.

The concept that electrocardiographic abnormalities identify those at higher risk of sudden death is not new. Initial investigations of this thesis in population studies supported the concept but included individuals with known ischaemic heart disease.[15 16] Though there is now stronger evidence supporting the prognostic ability of the electrocardiogram in persons with ischaemic heart disease,[17] there remain limited data on this subject in apparently healthy individuals.

The results of the present study are consistent with data from Life Assurance Companies that used as the end point primarily total mortality. ST segment and T wave abnormalities were associated with an increased subsequent mortality in several studies[18–20] as well as an increased incidence of myocardial infarction and mortality from that cause.[20] Left ventricular hypertrophy[18] and ventricular extrasystoles[18 21 22] were both associated with an increased mortality rate. With regards to epidemiological studies of apparently healthy men, most of them have focused on total ischaemic heart disease mortality and not on the incidence of sudden death. The adverse prognosis for ST segment and T wave abnormalities has been identified by others.[23 24] There is supporting evidence for left bundle-branch block as an adverse prognostic sign[23 24] which was observed in the Framingham population when persons with and without cardiac disease were combined.[25] The strength of the relation of ventricular extrasystoles to mortality herein was similar to one study,[26] and greater than several studies[14 23 24] though similar trends were seen in some.[23 24]

The value of left ventricular hypertrophy in prognosis observed herein is more consistent with the reports from the Framingham study[27] than with others.[23 24] There may be two explanations for this. Studies reporting no value of left ventricular hypertrophy included limb lead criteria of R amplitude greater than 20 mV in any of leads I, II, III, or aVF while our study and the Framingham study did not use this criterion. In addition, the present study suggests a potential explanation for the apparent differences of opinion as it applies to left ventricular hypertrophy. The Framingham study criteria included not only QRS voltage but also ST and T wave abnormalities,[14 27] while other studies used only voltage criteria.[23 24] We found that the association between sudden death and left ventricular hypertrophy increased with the presence of ST segment and T wave abnormalities. Detailed evaluation of ventricular extrasystoles[28] or left bundle-branch block characteristics[29] were not of benefit in increasing ability to predict sudden death. A comparison with two British studies that evaluated the prognostic value of the electrocardiogram is of interest. Tunstall Pedoe[30] followed, over a four-year period, a cohort of men aged 40 to 59 years, which included those with no evidence of ischaemic heart disease who had been employed in industry and took part in a cardiovascular screening programme. Rose *et al.*[23] determined five year total ischaemic heart disease mortality, which included sudden death, in a cohort of male civil servants aged 40 to 64 years. The results of our study and these two[23 30] agree that ST segment and T wave abnormalities on the resting electrocardiogram are important predictors of mortality. The importance of left bundle-branch block in our study is consistent with the report of Rose *et al.*[23] but not of Tunstall Pedoe.[30] In contrast to both of these studies[23 30] but not others[26] we found an increased risk of sudden death in persons with ventricular extrasystoles. The value of combinations of electrocardiographic abnormalities for the identification of subsets with increased risk of sudden death is similar to the findings of Tunstall Pedoe.[30]

The findings of the present study that 71% of cases of sudden death had a previous abnormal electrocardiogram must be interpreted within the context of repeated electrocardiographic examinations but indicate that the electrocardiogram is a relatively sensitive test in prediction of sudden death. ST segment and T wave abnormalities were the most frequently observed, consistent with the findings of Rose *et al.*[23] who commented that "even minor T wave inversion or flattening . . . being predictors even when it was the only recorded abnormality". The high prevalence of these electrocardiographic abnormalities, however, in conjunction with the low incidence of sudden death in apparently healthy men results in a low specificity. Thus a relatively small proportion of men with abnormal electrocardiograms will die suddenly. The absence of data on the potential benefit of identifying these subsets may not result in changes in case management. If the thesis is correct, however, that the ultimate control of ischaemic heart disease mortality in the community will depend on prevention rather than specific therapy for the event, then the identification of high risk groups from electrocardiographic variables may suggest individuals for investigation and evaluation of research strategies for prevention of sudden death.

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Predictive use of routine 24-hour electrocardiography in suspected Adams-Stokes syndrome

Comparison with cardiac rhythm during symptoms

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SUMMARY Using strictly defined criteria of significant arrhythmias, long term electrocardiographic recording has been evaluated for confirmation of arrhythmias as the cause of cerebral symptoms in 81 patients with suspected Adams-Stokes syndrome.

Extension of long term electrocardiographic recording for more than 24 hours gives marginal additional information at a high cost. Among 43 patients monitored until symptoms appeared, non cardiogenic causes were confirmed in 20 of 22 patients because the recording showed normal rhythm during symptoms. Fifteen of 21 patients with a significant arrhythmia during an asymptomatic 24 hour recording later had the same arrhythmia during symptoms.

Of 38 patients who failed to develop symptoms, 21 had a significant arrhythmia detectable within 24 hours and 23 when 48 hours of recording were analysed.

Long term electrocardiographic recording has disclosed that 20 to 75% of patients with suspected Adams-Stokes syndrome have serious arrhythmias known to or presumed to correlate with cerebral symptoms.[1-22] The varying rates of positive findings might be explained by differences in patient selection. Variations in duration of long term electrocardiographic recording and criteria for serious arrhythmias should also be considered. Lopes *et al.*[23] observed a moderate increase in ectopic beats while Jonas *et al.*[13] observed an increase in pertinent arrhythmias from 14 to 23% as long term electrocardiographic recording was extended from 12 to 24 hours. Kennedy *et al.*,[24] however, found that most instances of ventricular arrhythmias were correctly graded within 24 hours. Less is known about the increased detection of bradycardias as long term electrocardiographic recording is prolonged, but Tzivoni and Stern[25] reported that most cases with bradycardias severe enough to require pacemaker treatment were detected within 24 hours. Prolongation of long term electrocardiographic recording until symptoms appear may establish a temporal relation between arrhythmias and symptoms or it may rule out the Adams-Stokes syndrome by recording a normal cardiac rhythm during symptoms.

The main purpose of the present study is to compare the cardiac rhythm during symptoms with the arrhythmias detected during a 24 hour long term electrocardiographic recording using strict criteria for significant arrhythmias. In patients who failed to develop symptoms we determined the increase of serious arrhythmias detectable by prolonging long term electrocardiographic recording from 24 to 48 hours.

Patients and methods

Each year about 1300 patients are referred to the Section of Cardiology because of suspected Adams-Stokes syndrome. Regardless of previous electrocardiographic findings all of them are subjected to a routine 24 hour electrocardiographic recording.

This study included 81 patients aged 15 to 86 years (mean 61±SD16) suspected of having Adams-Stokes syndrome. During a four month period they were all selected because of weekly or more frequent attacks of syncope (n=17), dizziness including presyncope (n=45), or both (n=19). All patients had consented to wear an electrocardiographic tape recorder until symptoms had occurred and were expected to keep a diary noting the time of symptoms. Patients with recent changes in their cardiac medication were excluded. An examination was performed before the study in order to detect possible non-cardiac causes of

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symptoms. All patients participated for at least 48 hours but 38 patients terminated recording before symptoms because of subjective discomfort.

A previous myocardial infarction was suffered by eight patients while seven others were treated with digitalis and/or diuretics because of heart failure. Seventy-three patients were in sinus rhythm and had no pertinent arrhythmias detectable in their routine 12 lead electrocardiograms. One patient had atrial fibrillation with appropriate ventricular rates, while six had sinus rhythm plus ectopics or episodes of tachycardias, and one had a bradycardia of 50 beats per minute (bpm) or less (sinus bradycardia).

LONG TERM ELECTROCARDIOGRAPHIC RECORDING

Long term electrocardiographic recording was performed using portable electrocardiographic tape recorders type SRA/HRB-3 (Helcomed Norden/Hellige). The patients revisited the Section of Cardiology every second day for a technical check-up.

SCREENING OF ELECTROCARDIOGRAPHIC TAPES

The tapes were screened by one of two automatic units. One unit writes out all rhythms corresponding to rates faster than 120 or slower than 40 bpm, detected by a single RR interval, as a one-channel electrocardiogram on a paper strip. Write-out from the other unit is triggered by an increase or decrease of the cycle length of 30% or more of the average from the last minute of recording. In addition, both units write out every 10th ventricular extrasystole occurring within one minute of recording as detected by QRS configuration criteria. All electrocardiographic write-outs were screened by a specialised laboratory technician and one of the authors (N-J A).

CLASSIFICATION OF ARRHYTHMIAS

Arrhythmias known or presumed to correlate with cerebral symptoms were termed *significant*. Minor arrhythmias expected to occur in asymptomatic elderly subjects were classified as *insignificant* and omitted from this presentation.

The criteria of significant arrhythmias were based on the findings made when 103 elderly subjects (mean age 71±11 years) selected at random from the general population were examined by 24 hour long term electrocardiographic recording using the same equipment and screening limits.[26] The following arrhythmias were termed significant: frequent ventricular extrasystoles whenever one was followed by a second ventricular extrasystole within no more than five beats and this second extrasystole was followed by a third extrasystole within no more than five complexes, potentially dangerous extrasystoles[27] being observed separately; atrial tachycardias at a rate of ≥120/min and duration >8 s. The sick sinus syndrome was diagnosed according to one or more of the following criteria: (1) Sinus bradyarrhythmias ≤50 bpm and with a variation in consecutive PP intervals of ≥20%; (2) regular sinus bradycardia ≤45 bpm when awake; (3) sinoatrial block; and (4) sinus arrests of ≥1·5 s. The lowest rates were calculated from a sequence of three or more beats of the basic rhythm. Patients with the sick sinus syndrome and additional episodes of atrial tachyarrhythmias were considered to have the bradycardia-tachycardia syndrome.

Second and third degree atrioventricular block was always significant. In atrial fibrillation third degree block was designated if the ventricular rate, as calculated from three or more consecutive beats, was ≤40 bpm or 41 to 50 bpm with a QRS morphology different from that of conducted beats.

Results

The 81 participating patients were divided into two groups. One group consisted of 43 patients who tolerated long term electrocardiographic recording until symptoms appeared and one group of 38 patients terminating long term electrocardiographic recording at varying times ≥48 hours but before symptoms. Examination continued for two to 21 days (mean four).

PATIENTS WITH SYMPTOMS DURING LONG TERM ELECTROCARDIOGRAPHIC RECORDING

Among the 43 patients with symptoms 28 had syncope or dizzy spells. In 15 patients the symptoms during recording were cardiac but often connected with a sensation of pending collapse or associated with the onset of typical cerebral symptoms.

The arrhythmia diagnoses during the 24 hour periods and the number of patients with symptoms are shown in Table 1 together with patients with a normal rhythm during symptoms.

During the asymptomatic period 22 patients had no significant arrhythmias. A non-cardiac cause of their symptoms could be confirmed in 20 (91%) patients who had no significant arrhythmia during the entire 24 hour period during which symptoms occurred. Two patients lacking significant arrhythmias during the initial 24 hour period had atrial tachyarrhythmias when symptoms later developed (Table 1).

Twenty-one patients had significant arrhythmias suggesting a cardiac origin during the asymptomatic period. When symptoms appeared it was confirmed that the same arrhythmia previously recorded was related to symptoms in 15 (71%) of them. Furthermore, one patient with atrial tachyarrhythmias both initially and during symptoms had episodes of sinus bradycardia unrelated to symptoms during the same

Table 1 *Patients' examined by long term electrocardiographic recording until appearance of symptoms: Comparison of arrhythmia diagnosis from routine 24 hour recording with recordings when symptoms occurred*

Arrhythmia diagnosis	*Asymptomatic (routine) 24 hour period*	*Symptomatic 24 hour period*		*Patients with normal rhythm symptoms*
		Same arrhythmia	*Other arrhythmia*	
Not significant	22	20	2 (atrial tachyarrh)	20
Atrial tachyarrhythmias	7	6	1 (SSS)	2
Sick sinus syndrome:				
Brady-tachy	6	6	0	1
Brady only	1	1	0	1
Atrioventricular block, third degree	1	1	0	0
Frequent ventricular extrasystoles	2	2	0	1
Couplets ventricular extrasystoles/ventricular tachycardia	4	4	0	1

24 hour period in which symptoms occurred. This allowed the correct diagnosis of a bradycardia-tachycardia syndrome.

In six of the 21 patients who had significant arrhythmias during the initial period, symptoms did not occur simultaneously with the arrhythmias. One of these patients, however, later reported the disappearance of cerebral symptoms after pacemaker implantation and three reported the disappearance of symptoms on antiarrhythmic medication.

In 13 of the 15 patients with simultaneous arrhythmias both initially and during later symptoms the arrhythmias observed in connection with symptoms were of the same type and severity as those previously observed during the asymptomatic period. Notable aggravations of pre-existing arrhythmias were observed in only two cases as they fainted: one with couplets of ventricular extrasystoles developed ventricular tachycardia and one with third degree atrioventricular block had an asystole of 21 seconds.

A new type of additional significant arrhythmia was discovered during the period in which symptoms occurred in three patients. They had frequent ventricular extrasystoles temporarily unrelated to symptoms.

Use of less strict criteria for significant arrhythmia

Among the 20 patients with no significant arrhythmia at any time during the recording (including during symptoms—Table 1) eight had moderately frequent ectopic beats, two had atrial tachyarrhythmias lasting for a few seconds unrelated to symptoms, and four had a perfectly regular sinus bradycardia at the time of sleep. Among six patients with a bradycardia related to symptoms, three had moderately frequent ectopic beats and two had tachyarrhythmias lasting for a few seconds without relation to symptoms.

PATIENTS WITHOUT SYMPTOMS DURING LONG TERM ELECTROCARDIOGRAPHIC RECORDING

Thirty-eight patients had no symptoms during monitoring. Nineteen had no significant arrhythmias during the intitial 24 hour period, 18 (95%) of them remaining free from significant arrhythmias when long term electrocardiographic recording was extended to 48 hours. The one patient discovered by prolonging the period of recording had atrial tachyarrhythmias, and the remaining five patients with atrial tachyarrhythmias were discovered within 24 hours of long term electrocardiographic recording. All eight patients with the sick sinus syndrome, all three with second or third degree atrioventricular block, and both patients with ventricular arrhythmia were detected during the first 24 hours of recording. Three patients, however, with significant arrhythmias during the first 24 hours had the additional finding of ventricular arrhythmia as long term electrocardiographic recording was extended from 24 to 48 hours (Table 2).

Discussion

The clinical management of patients with cerebral symptoms and episodic cardiac arrhythmia has of necessity been empirical unless a temporal relation between arrhythmias and symptoms could be established. The present study investigated the adequacy of a routine 24 hour electrocardiographic recording using strict criteria for significant arrhythmias by comparing the arrhythmias initially present with the cardiac rhythm during later symptoms.

ARRHYTHMIAS DURING INITIAL (ROUTINE) 24 HOURS VERSUS RECORDINGS DURING SYMPTOMS

Among the 43 patients with electrocardiographic recordings until symptoms appeared, the asymptomatic periods included no significant arrhythmia in 22. By recording the cardiac rhythm during symptoms a non-cardiac cause of symptoms could be confirmed in 20. Thus, with the presently used classification of significant arrhythmias a negative routine 24 hour long term electrocardiographic recording gave a 91% prediction that the rhythm during symptoms would be normal.

Table 2 *Patients without symptoms during monitoring: comparison of arrhythmia diagnosis (significant arrhythmias only) present durng initial 24 hour period with arrhythmia diagnoses when second 24 hour period included*

Arrhythmia diagnosis	*From initial 24 hour period*	*With second 24 hour period included*		*New additional significant arrhythmia*
		Same	*Other*	
No significant arrhythmia	19	18	1 (atrial tachy)	
Atrial tachyarrhythmias	5	5	0	1 ventricular extrasystoles
Sick sinus syndrome				
Brady-tachy	4	4	0	1 ventricular extrasystoles
Brady only	4	4	0	
Atrioventricular dissociation	1	1	0	
Atrioventricular block second/third degree	3	3	0	1 ventricular extrasystoles
Frequent ventricular extrasystoles, couplets	2	2	0	

When the 24 hour recording suggested that arrhythmia was the cause of symptoms this was confirmed in 15 of 21 patients (71%) by recodring the same arrhythmia during symptons. Four of six patients, however, with significant arrhythmias not coinciding with symptoms improved on antiarrhythmic therapy. This improvement may have been spontaneous and the cause was not investigated further. Hence a routine 24 hour recording with significant arrhythmia was either confirmed or, using the terminology of Ward *et al.*,[22] clinically useful in 90% of the cases.

The managment of patients with significant arrhythmias is frequently based on the presumption that the arrhythmias documented are the antecedents of more serious arrhythmias. Among our 15 patients with simultaneous arrhythmia and symptoms this was only observed in two. The remaining 13 patients showed a varying response to the same arrhythmia.

Three previous reports[16 19 22] have demonstrated temporal relations between arrhythmias and cerebral symptoms in less than 10% of patients, while other reports showed from 13 to 76%, but a considerable number of patients have no significant arrhythmia at any time of the recording including during symptoms. There is little doubt that the former deserves treatment for arrhythmias and that a non-cardiac cause should be sought among the latter. More difficult is how to treat patients with significant arrhythmias unrelated to time of symptoms. It is worth while noting that four of six such patients in this series may later have responded to treatment. Conversely in another series 35 out of 44 (80%) patients without treatment for significant arrhythmias had persisting cerebral symptoms.[28]

There are several possible explanations for the lack of correlation between arrhythmias and symptoms in patients who may really have the Adams-Stokes syndrome. As pointed out before[13] temporary impairment of memory is part of the disorder. There may be failure to report symptoms,[18] the incorrect timing of events, or difficulties in obtaining adequate diaries.[5 13 20 22]

A major reason for lack of correlation between arrhythmias and symptoms may be a broader definition of significant arrhythmias. The report of Clark *et al.*[19] with a low incidence of patients with temporal relation between symptoms and arrhythmia may be illustrative of this, since the same group also provided a detailed report of the application of their criteria for significant arrhythmias in an elderly asymptomatic population of 13 subjects.[29] No less than 10 of these 13 subjects had "significant" arrhythmias. With the criteria currently used only nine of 77 asymptomatic elderly subjects[26] had significant arrhythmias. Correspondingly, a high rate of positive correlation with later symptoms was obtained in this series.

PATIENTS WITHOUT SYMPTOMS DURING RECORDING

Eighteen of the 19 patients with an initial 24 hour recording remained free from significant arrhythmias as long term electrocardiographic recording was extended from 24 to 48 hours. Among the 19 patients with significant arrhythmias during the initial 24 hour period three had an additional type of significant arrhythmia during the second period; the arrhythmia was ventricular in all three. Thus, the originally detected types of significant arrhythmia were confirmed as the only ones in 84% of those having significant arrhythmias during the initial 24 hour period.

Remarkably little is known about the increased detection of all types of significant arrhythmias attainable by prolongation of long term electrocardiographic recording. Lopes *et al.*[23] and Jonas *et al.*[13] reported that extension of long term recording from 12 to 24 hours resulted in considerable increases in ventricular or pertinent arrhythmias, respectively.

Kennedy *et al.*[24] found that the overwhelming majority of ventricular arrhythmias were detected within 24 hours when a comparison with additional days of recording were made. Among the entire series of 81 patients we noted that 19 of 20 cases with bradyarrhythmias were detected within 24 hours, but three of 14 patients with atrial tachyarrhythmias required prolonged monitoring for their detection.

COMPARISON WITH ASYMPTOMATIC POPULATIONS

In patients not experiencing symptoms during long term electrocardiographic recording the evaluation may be assisted by comparison with findings reported from asymptomatic populations.

Several investigations[30-34] have shown that almost every young, middle-aged, or elderly individual will have some type of cardiac arrhythmia when the electrocardiographic recording is continued for a sufficient time. A further analysis, however, discloses that sinus bradycardia is extremely common in young subjects,[31 33] while it is rare among elderly subjects.[35]

Seemingly in contrast with these more or less epidemiological investigations some clinically active centres have found that serious episodic arrhythmias are rare among selected normal elderly subjects.[14 35 36] This centre reported the findings when 103 elderly subjects selected at random from the general population were examined by 24 hour long term electrocardiographic recording.[26] Twenty-six of them admitted syncope and/or dizziness while 77 did not. Twelve of the 26 symptomatic and nine of the 77 asymptomatic subjects had significant arrhythmias according to the classification currently used ($p<0.001$). This may explain why so many of our patients had coinciding significant arrhythmias and symptoms. The use of strict criteria derived from the population study may also explain the high degree of prediction achieved from an asymptomatic 24 hour recording.

ECONOMIC ASPECTS

The costs involved in extended recording were impressive when related to the additional information obtained. Each new case of significant arrhythmia cost 5·7 times that of a significant arrhythmia discovered during routine recordings. Facilities for long term electrocardiographic recording are limited and we have chosen to screen a large group of patients with possible Adams-Stokes attacks[37] with a 24 hour electrocardiogram rather than to concentrate resources on a small group of patients.

Conclusions

We conclude that the routine 24 hour long term electrocardiographic recording will be sufficient to detect most patients with Adams-Stokes syndrome. When strictly defined criteria for significant arrhythmias are applied, the need for recording until symptoms occur will be reduced. Prolonged monitoring should be used principally in patients with problems of differential diagnosis or when there is strong evidence of the Adams-Stokes syndrome despite an initial negative recording. Provided that long term electrocardiographic recordings are interpreted with an open mind, the routine application of a 24 hour period should be acceptable, with the understanding that prolonged monitoring may be needed exceptionally.

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Self-predicting stress tests

Predischarge modified stress testing after acute myocardial infarction

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SUMMARY The outcome of 50 consecutive modified predischarge exercise tests after acute myocardial infarction was predicted by three independent observers on the basis of ST segment displacement in the resting pretest 12 lead electrocardiograms. The mean predictive accuracy for the three observers was 82% for a positive test defined as additional ST segment depression or elevation ≥0·1 mV, and rose to 94% for a positive test defined as additional ST segment depression ≥0·1 mV alone. For the majority of patients, the test result was already apparent in the resting 12 lead electrocardiogram.

After acute myocardial infarction, the safety and usefulness in prediction of modified predischarge exercise electrocardiography have been documented in a large number of recent reports,[1–10] implying that the test is not merely desirable, but actually *de rigueur* in continued postinfarction management. For example, a recent editorial states that "not to do an exercise test before discharge is to ask the patient to do the treadmill test at home".[11] In our hospital, we used low-level exercise testing in the past and the outcome of this test frequently seemed predictable from the standard 12 lead control electrocardiogram. This study was undertaken to define the relation of the resting electrocardiogram to the outcome of predischarge exercise testing after acute myocardial infarction.

Subjects and methods

PATIENTS

We investigated 50 consecutive patients, 40 men and 10 women with mean age of 61·7 (range 33 to 82) years, who underwent modified exercise electrocardiography eight to 18 (average 13) days after acute myocardial infarction. All were clinically fit for discharge from the hospital on the day of testing. One patient with infarction and pre-existing left bundle-branch block was excluded from the study.

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EXERCISE PROCEDURE

After baseline tracings taken from them supine, sitting, erect, and after hyperventilation, patients walked the treadmill during two three minute stages at slopes of 5 and 10 degrees at a constant speed of 1·7 miles per hour. Leads aVF, V4, and V5 were continuously monitored with printouts at the end of each stage and at two, five, and 10 minutes after exercise. Full electrocardiograms were obtained before and at the end of exercise, and again at the end of the 10 minute recovery period. The exercise was discontinued for the standard indications[12] or when the heart rate exceeded 110 beats per minute.

ELECTROCARDIOGRAPHIC CRITERIA

A positive exercise test was predicted blindly from the resting electrocardiographic abnormalities agreed upon in advance by three independent observers before reading the electrocardiograms; no subsequent modifications were allowed. The only abnormalities (Fig.) used for the prediction were (i) ST segment depression 0·1 mV 80 ms after the J point, (ii) ST segment elevation 0·1 mV 60 ms after the J point except in leads V1 to V3, and (iii) ST segment elevation 0·3 mV in leads V1 and V2, and 0·2 mV in V3.

The outcome of the exercise test was reported by two other independent observers, neither of whom took part in the predictive study. Their criteria for a positive test consisted of ST segment displacement 0·1 mV 80 ms after the J point in at least three consecutive cycles during or after the exercise.

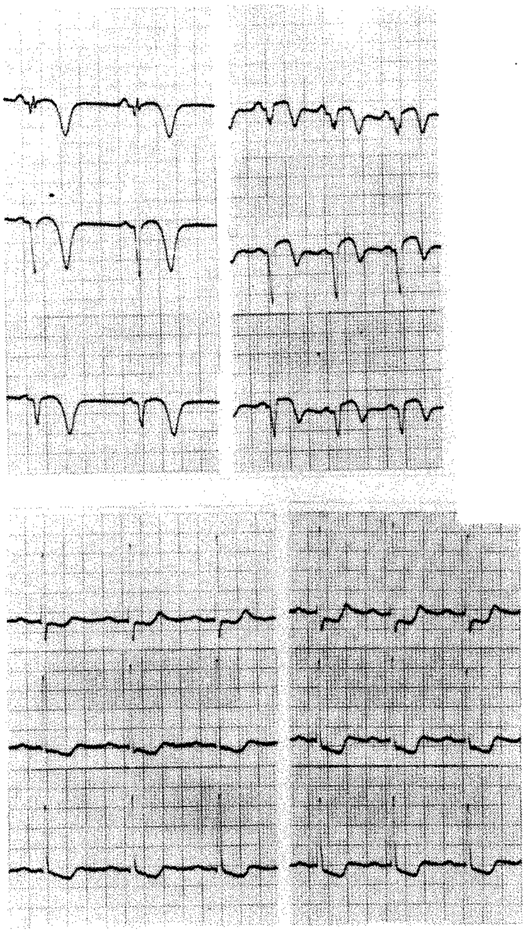

Fig. *Prediction of ST segment shift by the resting electrocardiogram. Above: leads aVF, V4, and V5 showing ST segment elevation at rest (left-hand panel) and further elevation with exercise (right-hand panel).* Below: *leads V4, V5, and V6 showing ST segment depression at rest (left-hand panel) and further depression with exercise (right-hand panel).*

STATISTICAL METHOD

The results were tested for differences by χ^2 analysis. Sensitivity, specificity, predictive value of a positive test, and accuracy were calculated for each observer by the standard formulae (Table 1).

Results

The procedure was completed in 45 out of 50 (90%) tests reviewed. Five incomplete tests (reported as inconclusive) were interrupted because of musculoskeletal pain, fatigue, or dyspnoea in the absence of ST segment criteria for a positive test. These five patients were significantly older than the remaining patients (mean age 72 vs. 60·5 years); their tests were excluded from the analysis.

There were no complications.

Of the 45 tests reaching a definite end-point, a mean of 37 (82%) were correctly predicted by the three observers from the pre-test resting electrocardiogram (Table 1). If additional ST segment elevation is not considered as "positive" (see Discussion), the figure rises from 82% to 94%.

No clinical or additional electrocardiographic features distinguished the patients whose tests were predicted correctly. In particular, the site of infarction (16 inferior, 13 anterior, six combined, and 10 without Q waves) had no effect on either the correctness of the prediction or the outcome of the test.

Comparison of the incorrect predictions (Table 2) among observers shows very little interobserver variation. This Table also shows that most false positive predictions were the result of the failure of the elevated ST segments to rise 0·1 mV further, while most false negative predictions involved ST segment depression.

Only three patients reported chest pain during the test (sharp left-sided pain in one); all three had a positive test with ST segment depression and the results of the exercise tests in these were correctly predicted from their resting electrocardiograms. An additional 14 patients had a "positive" test (nine with ST segment depression and five with ST segment elevation) without experiencing any symptoms.

Discussion

The data indicate that the resting electrocardiogram has a very high predictive value for the result of a modified predischarge exercise test after acute myocardial infarction, so long as there are minimal ST deviations in either direction (as defined in Subjects and methods section). A potential but unavoidable weakness of this study stems from its relatively conservative exercise procedure; on the other hand, more subtle criteria for prediction would have been required for more vigorous exercise. Our rate end-point of 110 beats per minute is lower than in the studies cited,[1-10] yet conforms to the rate target of Bruce's group in patients taking propranolol.[13]

None of the recent papers confirming[1-10] or denying[14] the prognostic value of modified exercise electrocardiography addresses itself to this comparatively simple electrocardiographic aspect of the test itself, though all involve eliciting otherwise hidden additional risk in their subjects. If this putative added risk can be inferred from the resting electrocardiographic abnormalities—as described long before the modified exercise electrocardiography test became popular[15 16]—the serious question arises as to the

Table 1 *Prediction of modified exercise electrocardiography test outcome by resting electrocardiogram*

Observer No.	*Electrocardiograph prediction*	*Modified exercise electrocardiography test*	*Statistical data*
1	18 +ve	14 +ve tests (TP)	Sensitivity 82%
		4 −ve tests (FP)	Specificity 89%
	27 −ve	24 −ve tests (TN)	Predictive value 78%
		3 +ve tests (FN)	Accuracy 84%
			χ^2 20·42017 with 2 degrees freedom and $p<0{\cdot}001$
			Contingency coefficient=0·4117940
2	17 +ve	13 +ve tests (TP)	Sensitivity 76%
		4 −ve tests (FP)	Specificity 86%
	28 −ve	24 −ve tests (TN)	Predictive value 76%
		4 +ve tests (FN)	Accuracy 82%
			χ^2 17·37099 with 2 degrees freedom and $p<0{\cdot}001$
			Contingency coefficient=0·3847086
3	16 +ve	12 +ve tests (TP)	Sensitivity 71%
		4 −ve tests (FP)	Specificity 86%
	29 −ve	24 −ve tests (TN)	Predictive value 75%
		5 +ve tests (FN)	Accuracy 80%
			χ^2 15·42788 with 2 degrees freedom and $p<0{\cdot}001$
			Contingency coefficient=0·3655929
Combined observers: mean sensitivity 76%, specificity 87%, predictive value (for a +ve test) 76%, accuracy 82%			

TP, true positive; TN, true negative; FP, false positive; FN, false negative.
Sensitivity, TP/TP+FN; specificity, TN/TN+FP; predictive value, TP/TP+FP; accuracy, correct/total predictions.

Table 2 *Incorrectly predicted tests*

Case No.	*Predictions* 1	2	3	*Cause of error*	*Test outcome*
13	+	+	+	No further ST segment elevation	−
15	+	+	+	No further ST segment elevation	−
33	+	+	+	No further ST segment elevation	−
42	+	+	+	No further ST segment elevation	−
12		−		Unpredicted ST segment depression	+
22	−	−	−	Unpredicted ST segment depression	+
23		−	−	Unpredicted ST segment depression	+
38	−	−	−	Unpredicted ST segment depression	+
50	−	−	−	Unpredicted ST segment depression	+

need for further testing in many, if not most, patients. It should be borne in mind that the extensively validated prognostic tests such as coronary angiography, contrast or radionuclide ventriculography, or 24 hour continuous monitoring are not in any sense replaced by the modified exercise electrocardiogram.

A second issue arising from this study is what should be called a positive test in patients with recent infarction. Evidence suggests that the predictable[17] ST segment elevation in leads with Q waves reflects wall dyskinesia rather than, simply, ischaemia,[18-20] but in view of the known significance of wall motion abnormalities[21] and their ischaemic aetiology such elevation may be reasonably held to constitute a positive test. On the other hand, this "positivity" is fairly regularly induced at higher heart rates in those with pre-existing ST segment elevation,[17] rendering interpretation difficult. Similar problems arise with ST segment depression from a depressed baseline, be it caused by "subendocardial" injury, hypertrophy, minor conduction defect, drugs, or electrolyte abnormalities. Since most electrocardiograms are abnormal after a recent infarction, it would be best, at this stage of knowledge, to desist from calling the modified exercise electrocardiograph tests either positive or negative, and to report them descriptively.

This study also shows that, out of 50 patients tested, only three had chest pain associated with ST segment depression; the others had negative, incomplete, or "electrically" positive test. It would be difficult to imagine great therapeutic potential in such findings. When many are tested for the sake of a few, the test is inefficient. The authors feel that it need not be used routinely.

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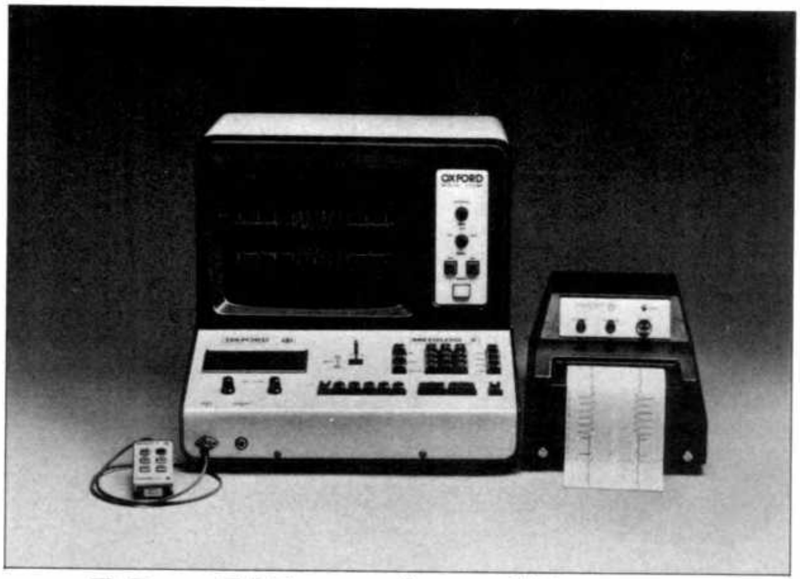

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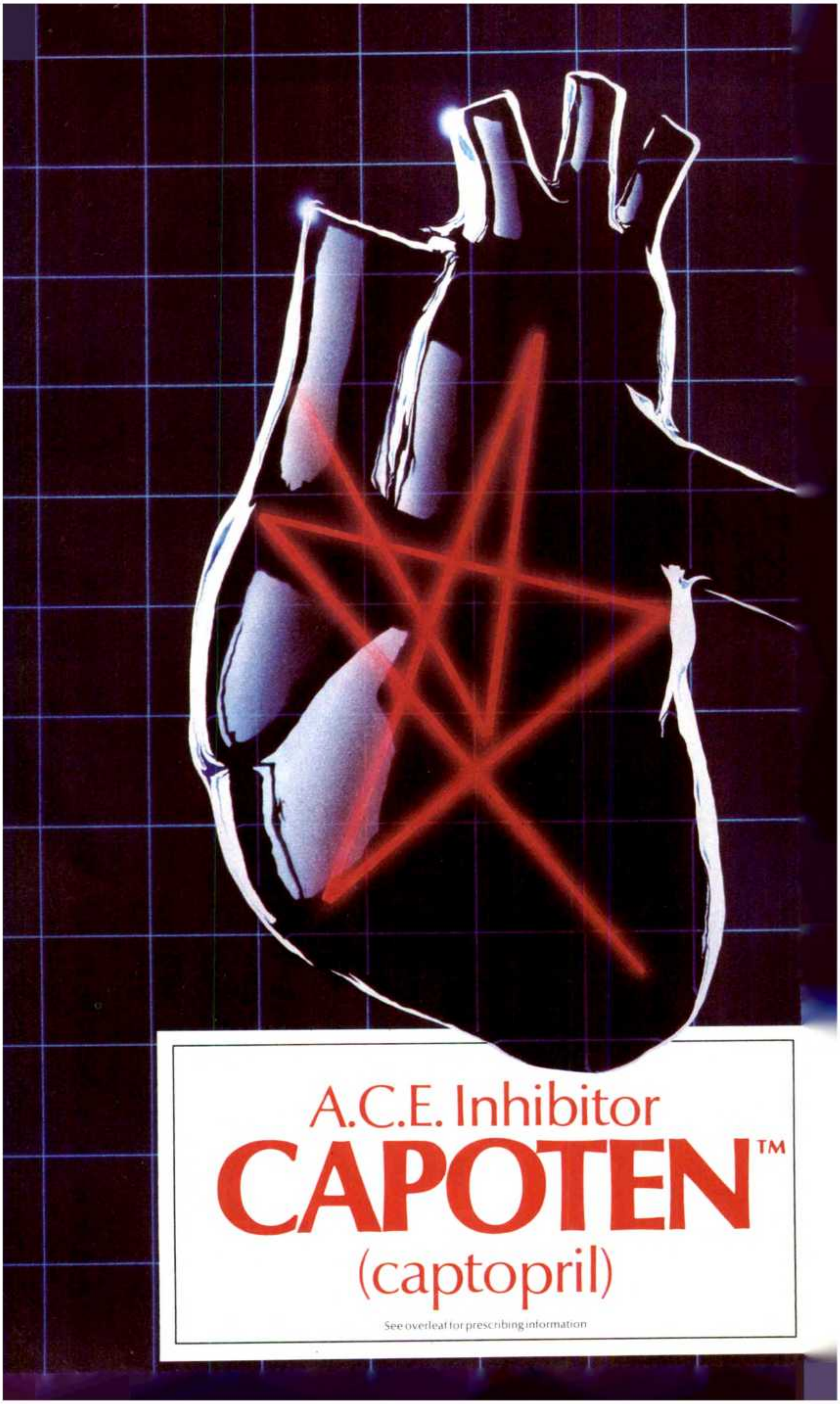

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CAPOTEN™ TABLETS Capoten tablets each contain 25 mg, 50 mg or 100 mg captopril. **USES** Capoten (captopril) in hypertension appears to lower blood pressure primarily by renin-angiotensin-aldosterone inhibition. Usage in hypertensive crises should be avoided. It has also been shown to be of benefit in the management of severe, treatment-refractory congestive heart failure. **Indications Hypertension** The treatment of severe hypertension where standard therapy has failed. **Congestive Heart Failure** Capoten is indicated for the treatment of severe, treatment-refractory congestive heart failure. The drug should be used together with diuretics and digitalis, but only after these agents have failed to produce a satisfactory response. **DOSAGE AND ADMINISTRATION** Capoten should be taken one hour before meals. **Adults Hypertension** The usual dose range of Capoten is 25-150 mg t.i.d. The maximum recommended daily dose is 450 mg. The initial daily dose of Capoten is 25 t.i.d. which should be increased to 50 mg t.i.d. if a satisfactory reduction of blood pressure has not been achieved in two weeks. If a satisfactory response has not been achieved after a further two weeks a modest dose of a thiazide diuretic (hydrochlorothiazide) or in patients with impaired renal function a loop diuretic (frusemide) should be added. The diuretic should be increased until a satisfactory response is obtained or its maximal dose is reached. Should Capoten 50 mg t.i.d. together with the diuretic fail to give a satisfactory reduction in blood pressure, then Capoten should be increased to 100 mg t.i.d., and then, if necessary, 150 mg t.i.d. For patients with accelerated or malignant hypertension, who are unresponsive to conventional therapy, it may be necessary to increase the daily dose of Capoten every 24 hours, until a satisfactory blood pressure response is obtained or the maximum dose of Capoten is reached. When Capoten is used alone, concomitant sodium restriction may be advantageous. Capoten may be used in conjunction with other antihypertensive agents, particularly thiazide diuretics and beta-blockers. **Congestive Heart Failure.** The usual starting daily dose is 25 mg t.i.d. and the usual effective dose range is between 25 and 150 mg t.i.d. After a dose of 50 mg t.i.d. is reached, further increases in dose should be delayed, where possible, for several weeks to determine if a satisfactory response occurs. Capoten should be used in conjunction with the highest usual doses of diuretic and with digitalis. Capoten therapy must be started in the hospital (see Warnings). A maximum daily dose of 450 mg of Capoten should not be exceeded. **Patients with Renal Impairment** About 75% of a given daily dose of Capoten is usually excreted in the urine; Capoten retention occurs in the presence of impaired renal function. The dosage interval should be increased as follows when creatinine clearance is below 75 ml/min/1.73 m^2:

Creatinine Clearance (ml/min 1.73 m^2)	Dosage Interval (Hours)
>75	8
75-35	12-24
34-20	24-48
19-8	48-72
7-5	72-108 (3 to 4.5 days)

When concomitant diuretic therapy is required, a loop diuretic (e.g. frusemide) is preferable to a thiazide diuretic.

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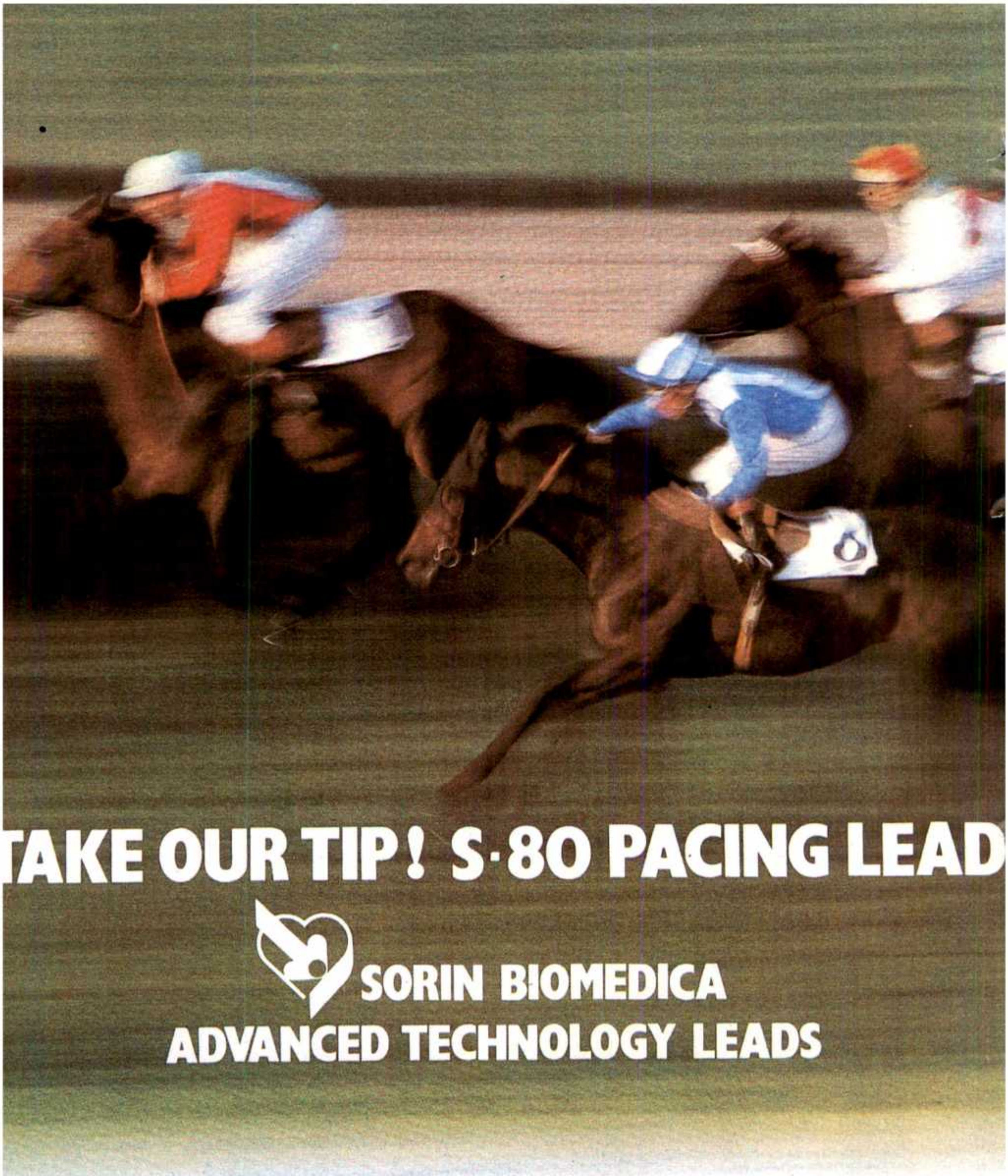

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Br Heart J 1982; 47: 563–72

Two dimensional echocardiographic assessment of communications between ascending aorta and pulmonary trunk or individual pulmonary arteries

J F SMALLHORN, R H ANDERSON,* F J MACARTNEY*

From the Thoracic Unit, The Hospital for Sick Children, Great Ormond Street, London

SUMMARY The value of two dimensional echocardiography in identifying communications between the ascending aorta and pulmonary trunk or individual pulmonary arteries was assessed in 24 children, all of whom had either angiocardiographic and surgical or angiocardiographic confirmation alone. Fourteen cases had truncus arteriosus, four aortopulmonary window, four anomalous origin of the left pulmonary artery from the ascending aorta, and two anomalous origin of the right pulmonary artery from the ascending aorta. It was possible to identify reliably each individual abnormality with a combination of suprasternal, precordial, and subcostal cuts. Problems only arose in differentiating truncus arteriosus from pulmonary atresia and ventricular septal defect when the main pulmonary artery and infundibular region of the right ventricle were extremely hypoplastic.

There are a number of abnormal communications in congenital heart diseases in which the pulmonary trunk or one or both pulmonary arteries communicate directly with the ascending aorta. These are truncus arteriosus, aortopulmonary window, and anomalous origin of one pulmonary artery from the ascending aorta. All of these conditions are unified morphologically by the presence of a defect between the ascending aorta and the pulmonary trunk or one or other pulmonary arteries. The aims of this study were to determine how these different conditions might be recognised and distinguished by two dimensional echocardiography.

Subjects and methods

The patients were drawn from those seen routinely at The Hospital for Sick Children, Great Ormond Street. There were 14 patients with truncus arteriosus. In all the diagnosis was prospective and had been confirmed by both angiocardiography and surgery. There were four patients with anomalous origin of the left pulmonary artery from the aorta. All had had angiocardiographic and surgical confirmation of the diagnosis. There were two patients with anomalous origin of the right pulmonary artery from the ascending aorta. In one the diagnosis was prospective and was confirmed at surgery; in the other it was retrospective after angiocardiography. There were four patients with aortopulmonary window; the diagnosis was prospective in two and retrospective in two others investigated elsewhere. All had angiographic confirmation of the diagnosis and in three surgical correction was undertaken. The fourth child died of severe pulmonary vascular disease before surgery. They were studied with an Advanced Technology Laboratory Mechanical Sector Scanner using either a 3·0 or 5 MHz scan head.

The transducer was initially placed so as to obtain a subcostal four chamber cut to assess the inlets of the heart and the size of the ventricular chambers. With clockwise rotation of the scan head a long axis of the left ventricle was obtained to assess its outlet and the presence of a ventricular septal defect. With continued clockwise rotation of the transducer the outlet of the right ventricle could be assessed.

Next the transducer was rotated anticlockwise back into the four chamber cut. With further anticlockwise rotation of the transducer, the outlet(s) from the left and right ventricles could also be assessed.

The scan head was next placed in the precordial position, so that a long axis cut of the left ventricle and its outflow tract was obtained. With slight clockwise rotation from the long axis the outlet of the right

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ventricle could also be seen. The transducer was then placed so as to obtain a short axis cut at the level of the papillary muscles of the left ventricle. Then, with anterosuperior angulation the mitral valve and outlet of the left ventricle could be visualised in their short axis. The scan was continued superiorly above the region of the semilunar valve to visualise any potential communication at this point.

Next, an apical four chamber cut was obtained and with anterosuperior angulation the outlet(s) of the heart and a ventricular septal defect, if present, could be seen.

The transducer was then placed in the suprasternal region so that the beam was parallel to the frontal and perpendicular to the sagittal plane of the body. In this cut the right pulmonary artery could be seen in its long axis, and its communication with the arterial trunk(s) assessed. The presence of an interrupted right pulmonary artery was also sought in this view. The transducer was next rotated clockwise or anticlockwise depending on the side of the arch. When the arch was visualised in its long axis, the head and neck arteries were identified as were any other arteries arising from it. In the long axis of the aortic arch the transducer was angled slightly downwards to visualise the aortic or truncal valves. With this manipulation any potential communication close to the semilunar valves could be identified. From the long axis position the transducer was angled towards the patient's left side in an attempt to visualise the left pulmonary artery.

Results

TRUNCUS ARTERIOSUS (14 cases)

In the subcostal four chamber cut a dilated left ventricle and left atrium were seen in all cases, reflecting the large left to right shunt. In the standard subcostal long axis cut of the left ventricle the truncus appeared to originate from the left ventricle alone (Fig. 1). Where one would expect to see a perimembraneous ventricular septal defect, a thick band of muscle (the ventriculo-infundibular fold) separated the truncal and tricuspid valves (Fig. 1). Only when the transducer was rotated slightly clockwise did the ventricular septal defect appear, reaching up to the truncal valve (Fig. 1). The truncal root was large and overrode the crest of the ventricular septum. With slightly further clockwise rotation it was evident that the same great artery formed the outlet of the right ventricle. In no case was a subpulmonary outflow tract found originating from the right ventricle, nor could the pulmonary trunk be traced as a separate structure running parallel to the main arterial trunk towards the base of the heart. In this cut the left pulmonary artery was seen in all patients originating from the posterior part of the trunk (Fig. 1). The left atrial appendage was seen in close proximity to the left pulmonary artery and trunk (Fig. 1). It was only with anticlockwise rotation of the transducer following the trunk towards the patient's right, that the take-off of both pulmonary arteries could be seen. The right pulmonary artery took an acute turn towards the hilum, while the left pulmonary artery followed a more gentle course (Fig. 2). Here again the left atrial appendage could be seen. The descending aorta could be seen in its short axis sitting between the two pulmonary arteries (Fig. 2). In this view it was again evident that there was no separate subpulmonary infundibulum in the right ventricle.

In the parasternal long axis cut the trunk overrode the crest of the ventricular septum in all cases. In one case the origin of the left pulmonary artery from the trunk was seen in this cut.

With slight clockwise rotation of the transducer from the long axis, the origin of the left pulmonary artery could be seen in all cases. With further rotation into the short axis both pulmonary arteries could then be assessed as they arose from the trunk (Fig. 3).

From the suprasternal cut the right pulmonary artery was seen in its long axis, with the aorta in its short axis in the initial cut in all but one case. In the latter there was absence of the right main pulmonary artery confirmed at cardiac catheterisation (Fig. 4a). The origin of the right pulmonary artery could be seen as the transducer was rotated anticlockwise towards the long axis of the aortic arch (Fig. 4b). In the long axis cut of the aorta, the origin of the left pulmonary artery could be seen in all cases as it arose above the valve (Fig. 5). The vessel was situated on the left posterior aspect of the trunk. The right pulmonary artery was not seen in this cut as it angled acutely back behind the aorta towards the right hilum. In no case was a pulmonary valve, or a pulmonary trunk separate from the aorta, identified. Surgical or necropsy confirmation of the diagnosis was available in all cases.

ORIGIN OF THE LEFT OR RIGHT PULMONARY ARTERY FROM THE AORTA: LEFT PULMONARY ARTERY FROM THE ASCENDING AORTA (4 cases)

Two patients had pulmonary atresia and ventricular septal defect with anomalous origin of the left pulmonary artery from the ascending aorta. In one the right pulmonary artery was only present in the hilar region, being supplied by major aortopulmonary collateral arteries. In the other case the right and main pulmonary arteries were hypoplastic.

Two cases had anomalous origin of the left pulmonary artery from the aorta, the right pulmonary artery being connected to the right ventricle via a normal outflow tract and the ventricular septum being intact.

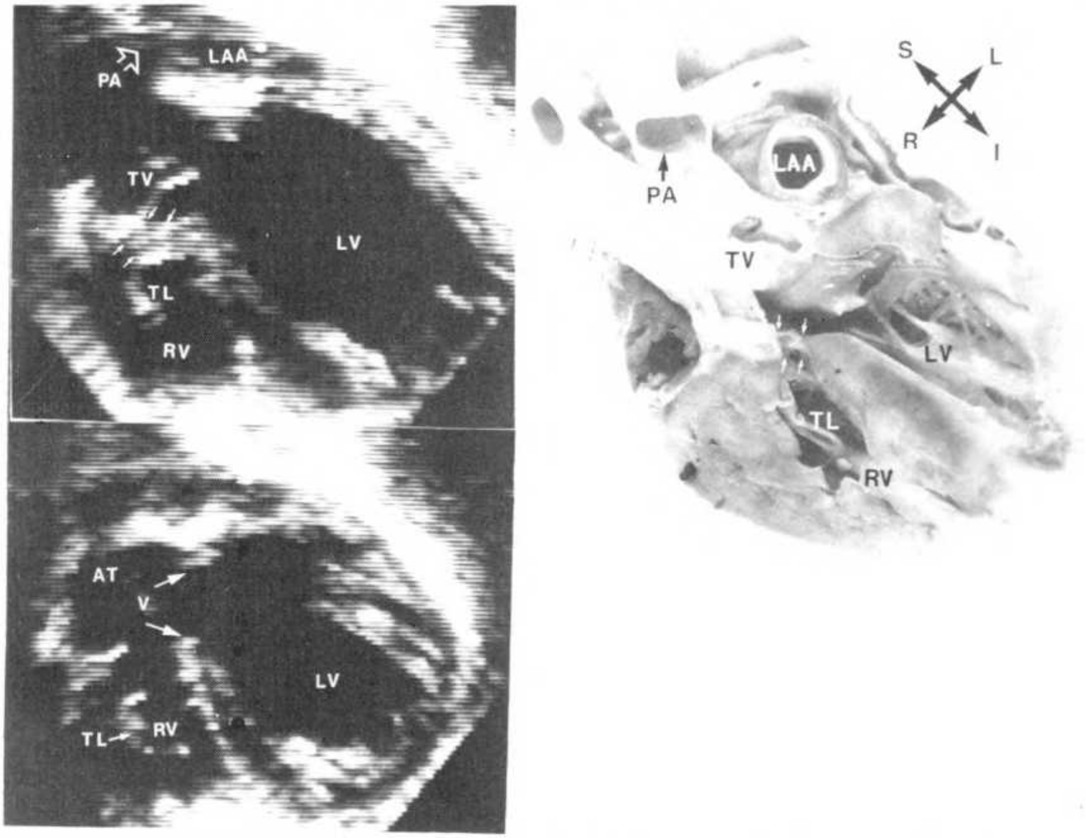

Fig. 1 *The upper left picture is a subcostal long axis cut in a case with truncus arteriosus. The small arrows show the ventriculo-infundibular fold separating the tricuspid valve and truncal cusps. Note the pulmonary artery arising from the lower aspect of the trunk. Also note the left atrial appendage. The specimen on the right is from the same case cut in the same plane. The lower picture is from the same patient with slight clockwise rotation to show the overriding trunk and the ventricular septal defect. AT, ascending trunk; LAA, left atrial appendage; LV, left ventricle; PA, pulmonary artery; RV, right ventricle; TL, tricuspid leaflet; TV, truncal valve; V, ventricular septal defect.*

In one patient there was an associated persistent ductus arteriosus supplying the right pulmonary artery.

In all cases the left pulmonary artery arose from the posterior aspect of the ascending aorta, just above the valve (Fig. 6). It was visualised in the subcostal long axis cut and in the precordial long axis cut with slight clockwise rotation. The aortic origin was also seen in both cases in the suprasternal view (Fig. 7).

In the patients with pulmonary atresia a large perimembranous outlet ventricular septal defect was present, with the aorta overriding the septum and providing the outlet of both ventricles (Fig. 6). When the transducer was rotated further clockwise an atretic pulmonary valve could be seen in one case supported by a subpulmonary infundibulum, with a small pulmonary trunk above it. In the other patient it was not possible to find a pulmonary trunk or subpulmonary infundibulum. In neither patient could the right pulmonary artery be seen.

In the two cases without pulmonary atresia, the pulmonary valve, pulmonary trunk, and right pulmonary artery were all seen subcostally. In the precordial short axis cut the right ventricular outflow tract was visualised as it wrapped around the aorta in both cases. The persistent ductus arteriosus in one was visualised from the suprasternal approach. Angiocardiographic and surgical confirmation of the diagnosis was present in all cases.

ANOMALOUS ORIGIN OF RIGHT PULMONARY ARTERY FROM THE ASCENDING AORTA (2 cases)

In both cases there was associated pulmonary atresia with ventricular septal defect. The pulmonary trunk and subpulmonary infundibulum were extremely

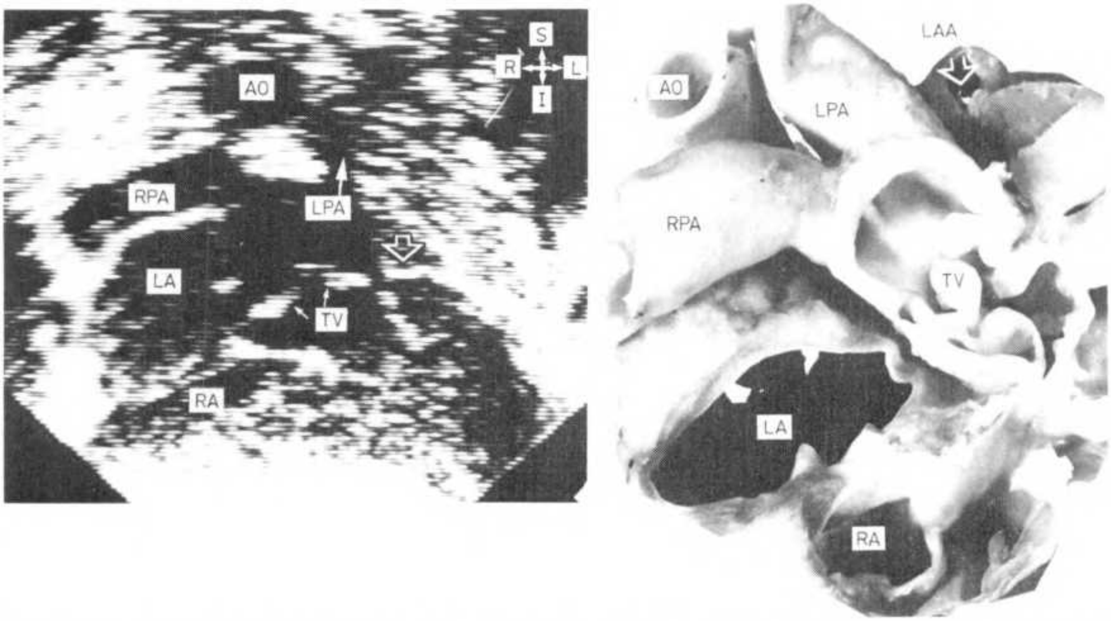

Fig. 2 *The picture on the left is a subcostal cut with anticlockwise rotation to visualise the origin of the pulmonary arteries. Note the right pulmonary artery takes an acute bend, while the left has a more gentle course. The specimen on the right is shown in the same plane. AO, aorta; LA, left atrium; LPA, left pulmonary artery; RPA, right pulmonary artery; TV, truncal valve.*

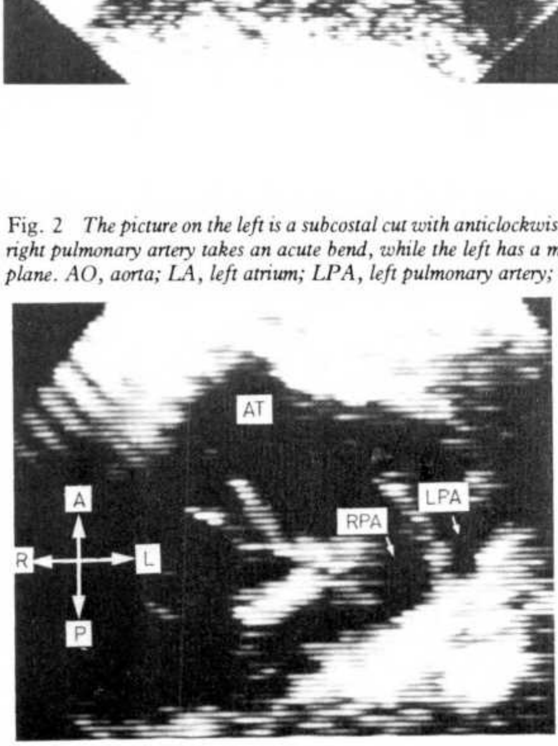

Fig. 3 *A precordial short axis cut to visualise the origin of the right and left pulmonary arteries. For abbreviations see Fig. 1 and 2.*

hypoplastic and could not be visualised echocardiographically. Angiocardiography disclosed a tiny pulmonary trunk with an atretic valve. In one case the left pulmonary artery was not connected to the pulmonary trunk, and was situated too distally to be visualised echocardiographically. The right pulmonary artery was seen arising from the ascending aorta in the suprasternal cut, originating more superiorly than in those cases with anomalous origin of the left pulmonary artery (Fig. 8). The origin of the right pulmonary artery could also be seen in the subcostal cut with anticlockwise rotation of the transducer.

In one of these cases there was an associated double aortic arch.

Regardless of which pulmonary artery originated from the aorta, the ventricular septal defect in patients with associated pulmonary atresia appeared in the subcostal long axis cut, and no ventriculo-infundibular fold was identified (Fig. 6).

AORTOPULMONARY WINDOW (4 cases)

Four cases were seen with aortopulmonary window, all with surgical or necropsy confirmation. In the suprasternal long axis cut of the aorta, the communication between the ascending aorta and main pulmonary artery could be seen in all cases (Fig. 9). The appearance was different from those cases with either truncus arteriosus or anomalous origin of the pulmonary artery from the aorta (compare Fig. 5, 6, and 9). As the lower border of the ascending aorta was followed superiorly the communication could be seen, appearing like a semicircle, instead of the usual circular pattern of the main pulmonary artery. In one patient a coexisting persistent ductus arteriosus (confirmed at surgery) was visualised by this approach.

In the precordial short axis cut with slight anterosuperior angulation, the window could also be visualised (Fig. 10). From the same cut the pulmo-

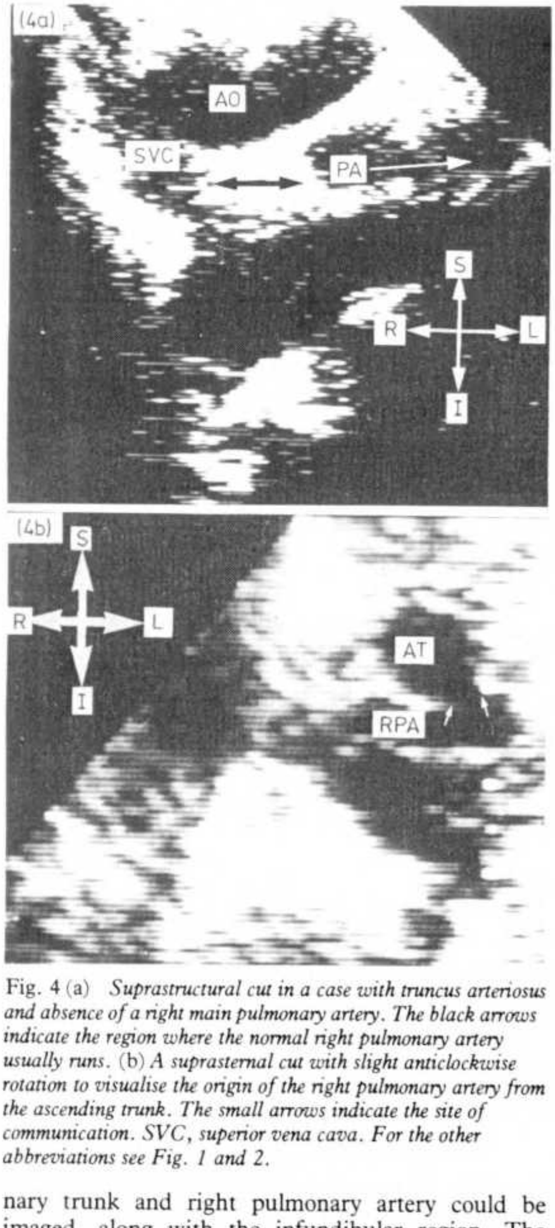

Fig. 4 (a) *Suprastructural cut in a case with truncus arteriosus and absence of a right main pulmonary artery. The black arrows indicate the region where the normal right pulmonary artery usually runs.* (b) *A suprasternal cut with slight anticlockwise rotation to visualise the origin of the right pulmonary artery from the ascending trunk. The small arrows indicate the site of communication. SVC, superior vena cava. For the other abbreviations see Fig. 1 and 2.*

nary trunk and right pulmonary artery could be imaged, along with the infundibular region. The widow was not seen in the parasternal long axis cut.

In the standard subcostal long axis cut the aortopulmonary window was seen in two cases. The window was reliably visualised in all four, only when the transducer was rotated anticlockwise into a position where the ascending aorta was seen in its long axis with the pulmonary trunk crossing it (Fig. 11). Care was required to avoid misinterpretation of the region where the right pulmonary artery and aorta crossed, as drop-out in this region could be mistaken for an aortopulmonary window. This was avoided by ensuring that only the region where the main pulmonary artery and aorta crossed was used to visualise the aortopulmonary window.

Discussion

The group of malformations described above has one anatomical feature in common, namely a communication between the ascending aorta and the pulmonary trunk or one or both pulmonary arteries. Angiographically, each would be characterised by direct opacification of either the pulmonary trunk, or the right or left pulmonary arteries from an ascending aortogram.[1,2] As it turns out, the logical process whereby these different anatomical substrates can be distinguished is precisely the same for cross-sectional echocardiography as for angiography.

The first step is to identify aortopulmonary window by demonstrating that two semilunar valves and two ventricular outflow tracts are present. To accomplish this, a precordial and subcostal cut should be used to demonstrate the ventricular outflow tracts and the separate arterial valves. The precordial cut in isolation[3] will diagnose aortopulmonary window in most cases, but has been misleading in our experience in a case of left coronary artery to coronary sinus fistula. This may seem at first sight surprising, but the appearances in the precordial short axis cut are remarkably similar. This experience emphasises the importance of always using multiple cuts, and identifying the origin of the coronary arteries from the aorta.[4]

The suprasternal cut is of great value as the appearance differs from cases with truncus arteriosus or anomalous origin of one pulmonary artery from the aorta. Normally the main pulmonary artery is seen as a circle, lying beneath the aortic arch. In patients with an aortopulmonary window a semicircle is present, the absent upper part representing the window.

The next step is to identify typical truncus arteriosus, in which both pulmonary arteries originate from the solitary arterial trunk sometimes via a short main pulmonary artery. This is easily achieved with angiography projections, and is equally readily shown echocardiographically. In the subcostal cut this is usually obvious. The subcostal long axis cut allows visualisation of the origin of the left pulmonary artery from the aorta. Care must be taken not to mistake the left atrial appendage for the other pulmonary artery (Fig. 12). The left atrial appendage lies in close proximity to the left pulmonary artery and can be seen entering the left atrium lying behind the ascending trunk. The appendage is also seen in patients with ventriculoarterial concordance, but the presence of the left pulmonary artery arising from the trunk with

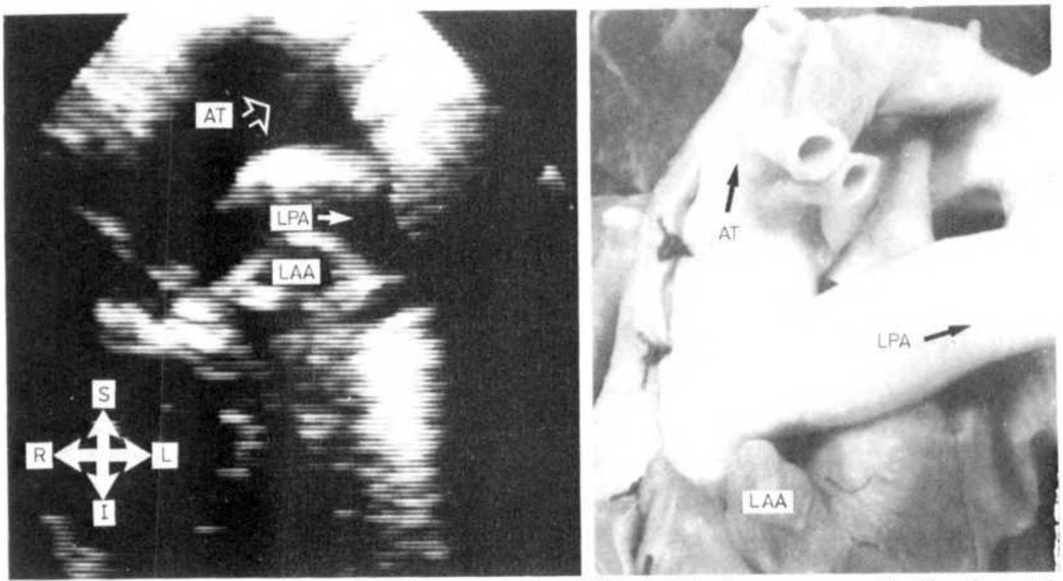

Fig. 5 *Suprasternal long axis cut in a patient with truncus arteriosus. Note the left pulmonary artery arising from the posterior aspect of the ascending trunk. In addition note the relation of the left atrial appendage to the left pulmonary artery. The specimen on the right is from the same case showing the echocardiographic features. For abbreviations see Fig. 1 and 2.*

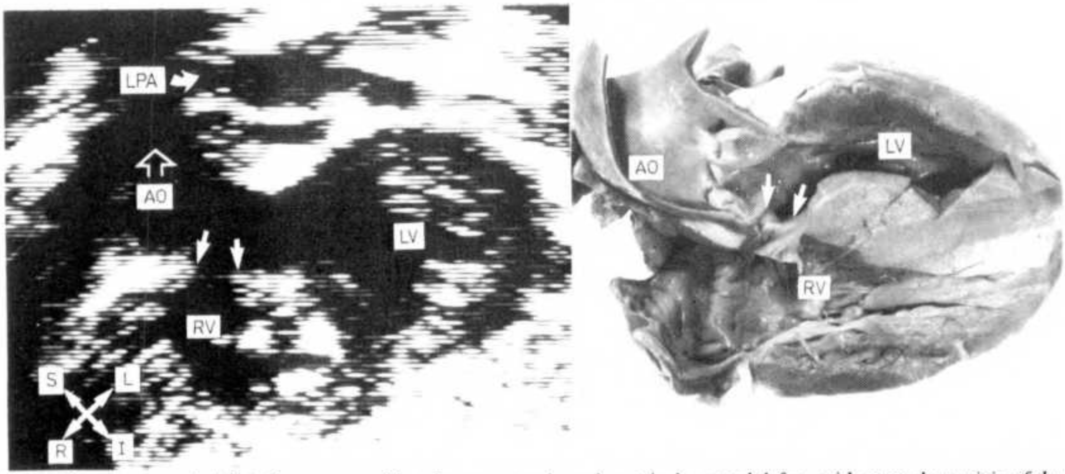

Fig. 6 *The picture on the left is from a case with pulmonary atresia and ventricular septal defect, with anomalous origin of the left pulmonary artery from the aorta. The arrows point to the ventricular septal defect. The specimen on the right is from a different case with pulmonary atresia and ventricular septal defect. Note the region of continuity between the tricuspid valve and aortic valve. For abbreviations see Fig. 1 and 2.*

the appendage overlapping it provides this misleading picture. Both pulmonary arteries may be visualised simultaneously when the transducer is rotated clockwise following the origin of the trunk. Likewise, further confirmation of bilateral truncal origin can be obtained in the precordial short axis cut.

What is harder to demonstrate by angiocardiography or echocardiography is the presence or absence of a short main pulmonary arterial segment. Echocardiographically, this is because the left and right pulmonary arteries form a sharp angle with one another, just as they do when they originate from a normal pulmonary trunk. In all the cases with right and left pulmonary arteries studied, the arteries arose directly from the solitary trunk, albeit in close approximation to one another. The echocardiographic techniques also all showed a single semilunar valve which in these cases overrode the ventricular septum. It must be

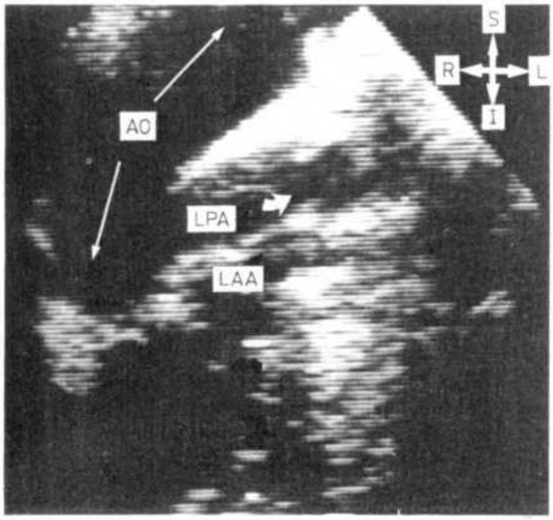

Fig. 7 *A suprasternal cut in a case with pulmonary atresia and ventricular septal defect with anomalous origin of the left pulmonary artery from the aorta. Note the appearance is similar to that seen in Fig. 5 in a case of truncus arteriosus. For abbreviations see Fig. 1.*

remembered, however, that monoventricular origin of a truncus has been described,[5 6] so overriding need not necessarily be present. In the hearts studied no evidence of a blind infundibulum from either ventricle was identified, nor was a second arterial trunk found extending from the base of the heart.[5]

In the suprasternal cut, it has been suggested[7] that the main pulmonary artery segment is imaged originating from the ascending trunk. Our anatomical studies, together with the well-recognised observation of a high arching left pulmonary artery in truncus arteriosus, suggest that it is usually the left pulmonary artery that gives rise to this appearance. This is important, since the very same feature is seen in anomalous origin of the left pulmonary artery alone in the absence of truncus arteriosus (compare Fig. 5 and 6). This of course would not apply in the case where there was a reasonable sized main pulmonary artery segment.

Aortopulmonary window and typical truncus arteriosus are therefore readily recognised. When only one pulmonary artery originates from the ascending aorta, however, two problems arise, one related to recognition of discontinuity of the pulmonary arteries, and the other to hypoplasia of one pulmonary artery.

The first problem is exemplified by those cases in which the left pulmonary artery arose from the ascending aorta, and the right from the right ventricle

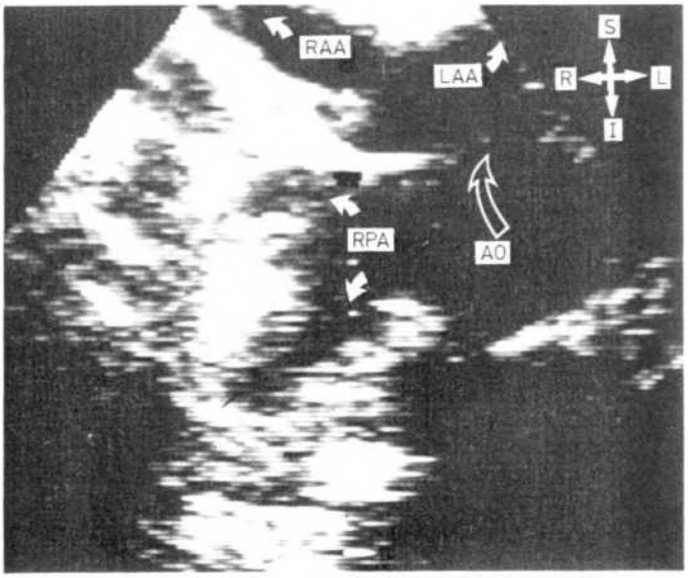

Fig. 8 *A suprasternal cut in a case with pulmonary atresia and ventricular septal defect with anomalous origin of the right pulmonary artery from the ascending aorta. This patient also had a double aortic arch. LAA, left aortic arch; RAA, right aortic arch. For other abbreviations see Fig. 2.*

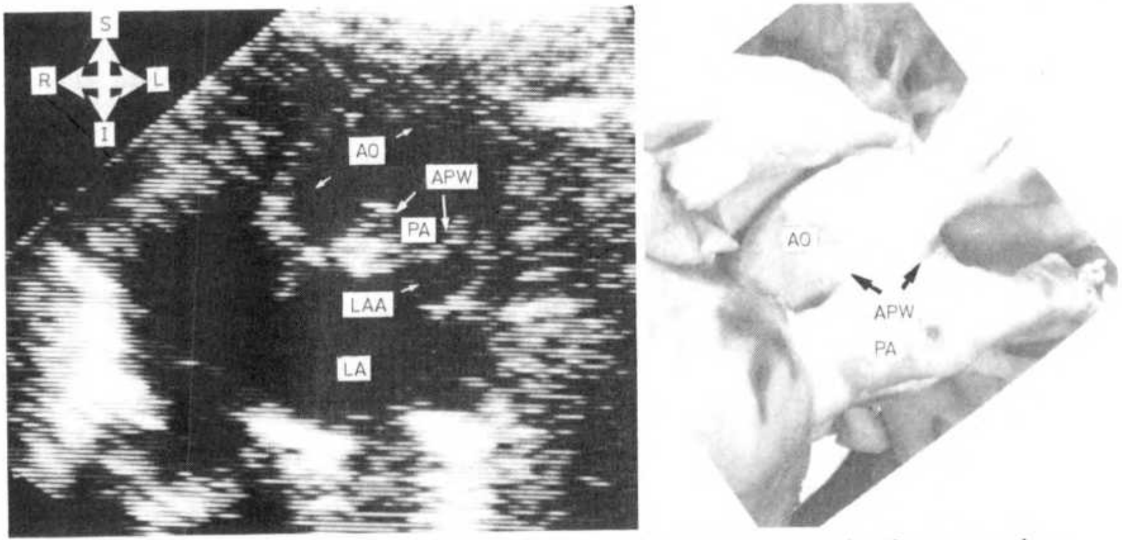

Fig. 9 *The picture on the left is a suprasternal cut in a case with aortopulmonary window. Note the pulmonary artery has a semicircular appearance, instead of its normal circular shape. The specimen on the right from a different case shows the aortopulmonary window. This patient also had an interrupted aortic arch. APW, aortopulmonary window. For other abbreviations see Fig. 1 and 2.*

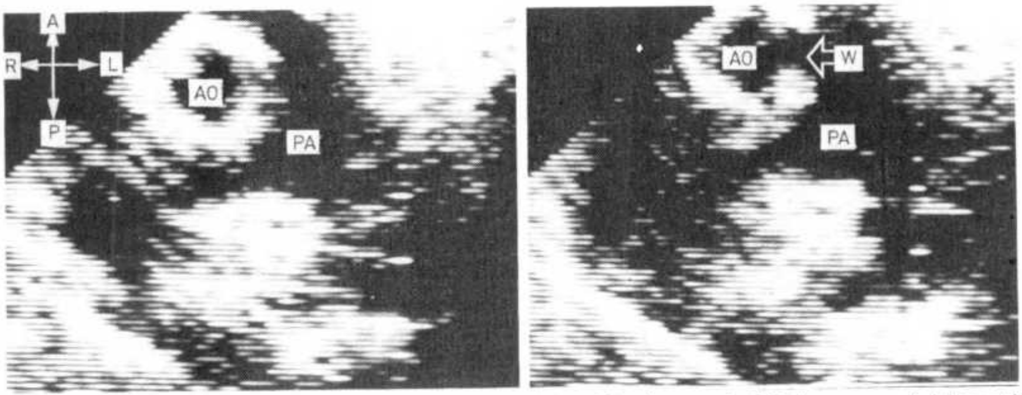

Fig. 10 *Precordial short axis cut in a case with aortopulmonary window. The picture on the left shows a normal right ventricular outflow tract. The image on the right is obtained with slight clockwise rotation to visualise the window. W, window. For other abbreviations see Fig. 2.*

in the presence of an intact ventricular septum. In the subcostal and precordial short axis cuts, the right pulmonary artery is well visualised in its normal position, and lack of demonstration of bifurcation of the pulmonary trunk may be incorrectly ascribed to the frequent and normal manner in which the left pulmonary artery turns out of the plane of the tomographic cut as it leaves the right pulmonary artery. This error may be avoided by using the suprasternal or high short axis view, provided that care is taken to trace the right pulmonary artery to the expected position of the left pulmonary artery. As the presumed site of the bifurcation is reached, the right pulmonary artery, instead of continuing into the left, appears to terminate abruptly. Though we have not observed cases with isolated anomalous origin of the right pulmonary artery from the aorta, we presume that this diagnosis would be readily made because of the abnormal appearance of the right pulmonary artery in the standard subcostal and precordial cuts.

The second problem, that of extreme hypoplasia of the pulmonary artery not arising from the aorta, occurs when there is an interventricular communication and pulmonary atresia. If the pulmonary outflow

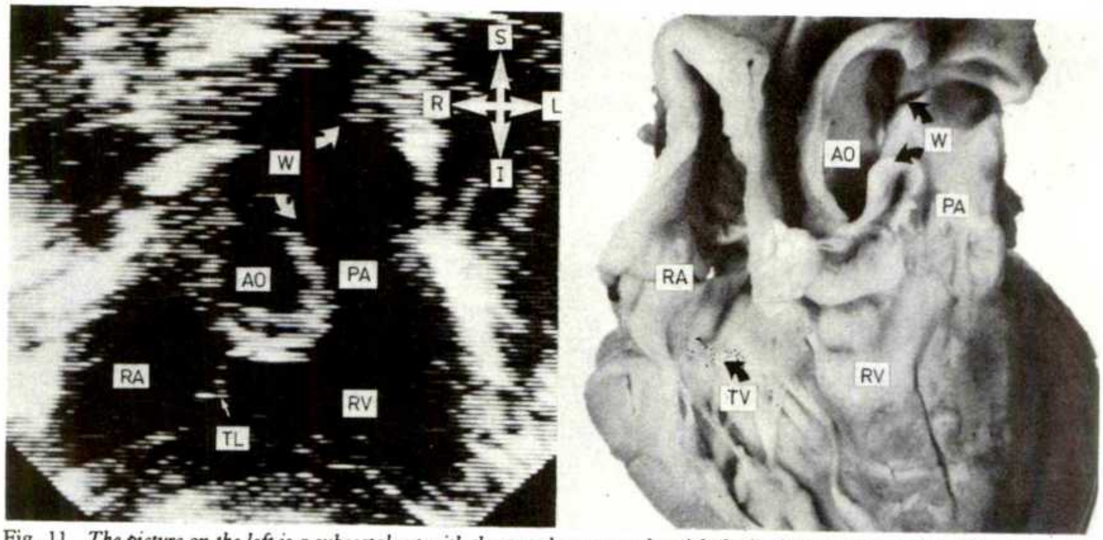

Fig. 11 *The picture on the left is a subcostal cut with the transducer rotated anticlockwise following the outlets of heart. Note the large window indicated by the arrows. The specimen on the right is from a different case, but cut in the same way to visualise the aortopulmonary window. RA, right atrium. For other abbreviations see Fig. 1, 2, and 10.*

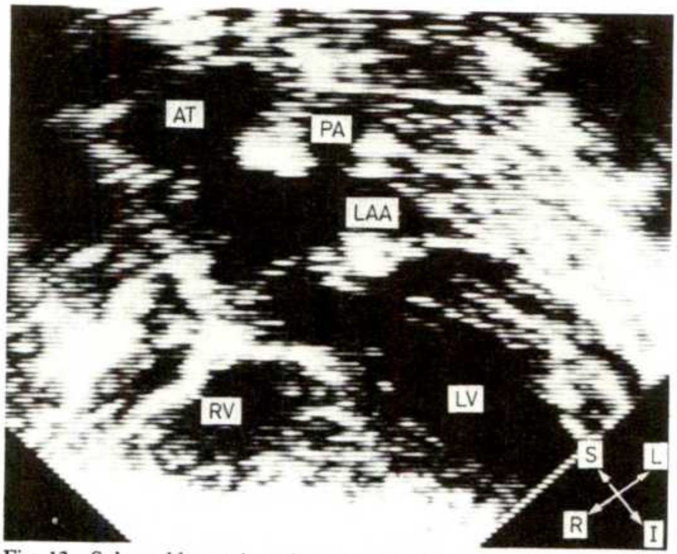

Fig. 12 *Subcostal long axis cut in a case with truncus arteriosus. Note the origin of the left pulmonary artery. Observe the left atrial appendage which overlaps the left pulmonary artery giving a false impression of truncal origin. For abbreviations see Fig. 1 and 2.*

tract is merely stenotic, then though the pulmonary trunk will be hypoplastic, it should be possible to identify it separately from the aortic trunk.

When there is pulmonary atresia, however, the pulmonary trunk may be so grossly hypoplastic (or atretic) as to be unidentifiable. Under these circumstances, just as with angiocardiography, it may be impossible to differentiate between pulmonary atresia with ventricular septal defect and truncus arteriosus.[5] Identification of a blind right ventricular outflow tract will then establish the diagnosis as pulmonary atresia with ventricular septal defect.[7] Failure to demonstrate such an outflow tract, however, does not necessarily establish the diagnosis of truncus, both because of the limits of resolution of the equipment and because in two out of 22 specimens of pulmonary atresia with ventricular septal defect studied at necropsy, no blind right ventricular outflow tract was found.[5] A further guide to differentiation between the two is demonstration of a ventriculo-infundibular fold separating the tricuspid from the arterial valve, since this was found in 51 out of 66 (77·3%) of cases with truncus, as opposed to four out of 24 (16·7%) with pulmonary atresia.[5] Finally, the demonstration of more than three semilunar valve cusps[8] favours the diagnosis of truncus. In cases of anomalous origin of one pulmonary artery from the ascending arterial trunk, however, the distinction between truncus and pulmonary atresia with ventricular septal defect is academic. What *is* important is to distinguish between absence of the contralateral pulmonary artery and atresia of it somewhere proximal to the hilum. If echocardiography cannot demonstrate the pulmonary artery arising from the ascending trunk, or show a persistent ductus running to the hilum on that side, then angiocardiography, possibly including pulmonary vein wedge angiography, will be the only method by which a hilar pulmonary artery, if present, can be demonstrated, short of exploratory surgery.

Thus, by the application of cross-sectional echocardiography, it is possible reliably to identify a defect between the ascending aorta and pulmonary trunk or one or other pulmonary arteries. Truncus arteriosus and aortopulmonary window are readily separated, as are those cases where a pulmonary artery arises anomalously from the ascending aorta in the presence of a normal main pulmonary artery and valve. Problems, however, may arise in differentiating truncus arteriosus from pulmonary atresia and ventricular septal defect when the main pulmonary artery and infundibular region of the right ventricle are extremely hypoplastic. This difficulty may also be encountered when using more traditional techniques of investigation.

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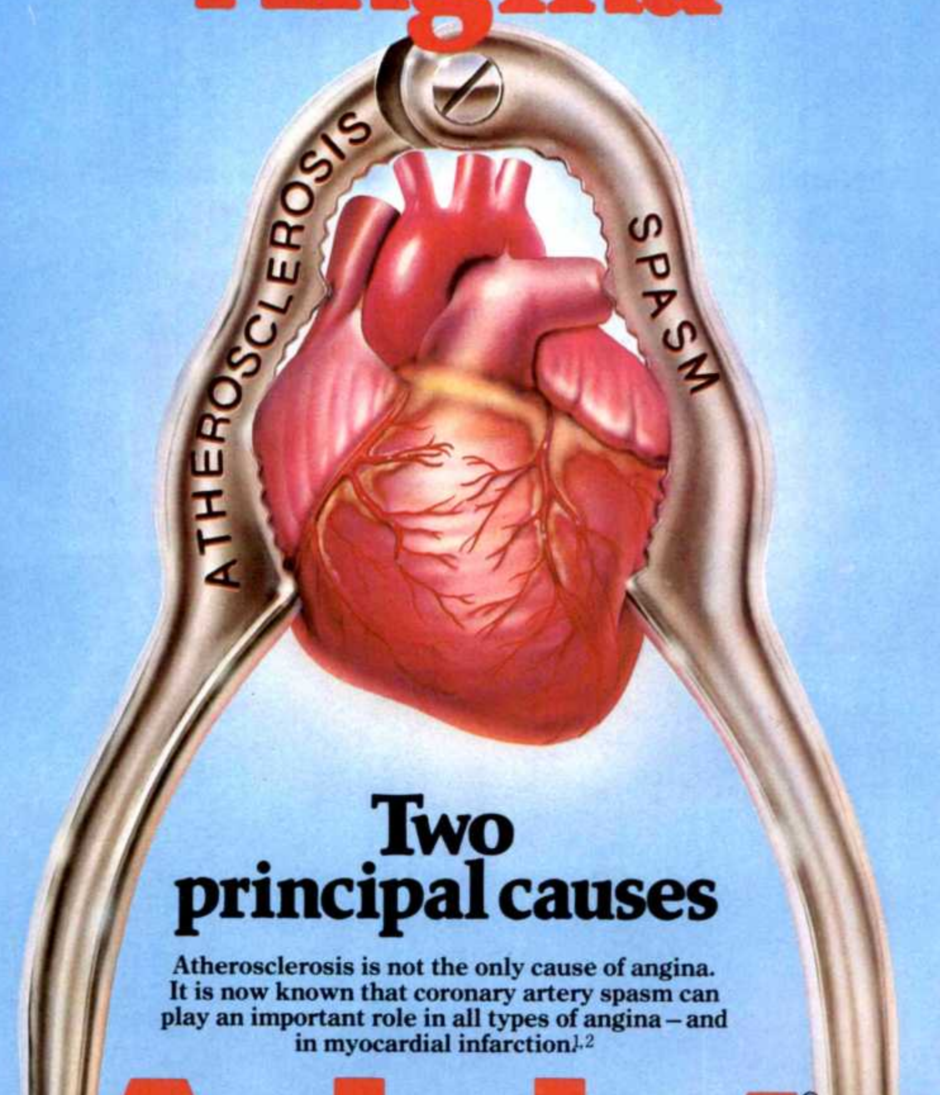
Angina



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References 1. *Brit Med J* 1979; **1** : 969-70 2. *Amer J Cardiol* 1979; **44** : 788-92 3. *Eur Heart J* 1980; **1** (Suppl B) : 71-85 4. *J Roy Soc Med* 1980; **73** : 570-5 5. 3rd International Adalat Symposium. Amsterdam – Oxford: Excerpta Medica, 1976: 303-5 6. *New England J Med* 1980; **302** : 1269-73 7. *Br Med J* 1980; **281** : 184-3

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Br Heart J 1982; 47: 573–83

M-mode echocardiography in the developing human fetus

LINDSEY D ALLAN, MICHAEL C JOSEPH, EDWARD G C A BOYD,
STEWART CAMPBELL, MICHAEL TYNAN

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SUMMARY The M-mode echocardiogram can be obtained in the developing human fetus from around the 16th week of gestation until term. Errors in interpretation of the M-mode echocardiogram can be avoided by concurrent two dimensional fetal cardiac examination. The pattern of motion of the mitral, tricuspid, aortic, and pulmonary valves and ventricular wall motion can be studied. Motion of the foramen ovale flap, which is characteristic in fetal life, can also be observed. Using the M-mode tracing, measurement data for six variables were made and growth charts constructed. The variables recorded were septal and left ventricular wall thickness, right and left ventricular internal dimension in diastole, aortic root dimension, and left atrial internal dimension. The measurements were made in normal pregnancies where the fetal heart was structurally normal. Confidence limits for each measurement were derived for gestational ages between 16 and 39 weeks.

The anatomy of the normal fetal heart can be visualised using realtime two dimensional echocardiography from around the 16th week of gestation until term.[1 2] During our continuing echocardiographic study for the prenatal detection of cardiac abnormalities it became apparent that it was also possible to record an M-mode echocardiogram. The M-mode allows the study of the pattern of motion of cardiac valves and wall movement. It allows clear definition of endocardial surfaces. These are difficult to define on a realtime frozen frame image which has been used by other authors for the acquisition of measurement data.[1] Measurements can be more precisely timed within the cardiac cycle on the M-mode echocardiogram. Standard measurements can be made that can be compared with postnatal data. In addition, functional variables can be derived as from the postnatal echocardiogram.

Once the anatomical structures and the orientation of the fetal heart have been identified it is possible to select the M-mode recording to be made by locating the M-line (ATL Mark III) through the structures to be studied. It is essential that two dimensional identification precedes the M-mode examination. This is because it can be impossible to differentiate the aortic from the pulmonary valve or the mitral from the tricuspid valves by their M-mode motion alone. It can also be difficult to differentiate right from left ventricular wall motion, especially in the early fetal heart.

Detailed fetal cardiac measurements are not as yet available and therefore we have compiled data for pregnancies between 16 weeks gestation and term. The measurements made were septal and left ventricular wall thickness, right and left ventricular internal dimensions, aortic root and left atrial dimensions.

Subjects and methods

Fetal M-mode echocardiograms have been obtained in 254 subjects. Ethical committee approval for this study was obtained. Originally the aortic root dimension only was measured in 54 subjects. It was subsequently realised that a complete M-mode echocardiogram could be attempted. This was done in 200 subjects. An Advanced Technical Laboratories Mark III sector scanner with a 3 MHz transducer was used. The two dimensional pictures were recorded on a Sanyo VTC 7100 video cassette recorder and the M-mode on a Honeywell black and white stripchart recorder operated at 50 mm/s.

In 48 cases a fetal electrocardiogram was also recorded on the M-mode tracing, using a purpose built isolated fetal electrocardiographic preamplifier

This research has been supported by the British Heart Foundation.

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connected to three abdominal electrodes.

The M-mode echocardiogram was studied and measurements made only in normal pregnancies where no structural abnormality of the fetal heart was apparent. The fetal age was determined by biparietal diameter measurements made early in pregnancy, that is before 20 weeks gestation, when this measurement is the most reliable determinant of fetal age.[3] Estimated gestational age by this means was felt to be the most useful correlate with cardiac measurements as the majority of our data lay between 16 and 28 weeks gestation. In this age range other fetal measurements such as derived fetal weight are less accurate.

Two dimensional echocardiographic identification of fetal cardiac chambers was performed initially. This is essential since it cannot be assumed that structures visualised closest to the transducer are anterior in the fetus. Nor can it be assumed that the fetus has a normal heart. Abnormalities of connections and relations must be excluded. Fortunately the unobstructed access to the fetal heart allows this to be accomplished using morphological criteria. The right ventricle is differentiated from the left by the coarser right ventricular trabeculations and the more apical insertion of the septal leaflet of the tricuspid valve. Fig. 1 shows a still frame demonstrating these features, the angulation of the tricuspid valve indicating its more apical septal insertion. This differentiating feature is seen more easily in the moving two dimensional image. The aorta is identified by showing its continuity from the left ventricle to the ascending aorta, aortic arch, and its branches. The pulmonary artery must be shown to connect the right ventricle to the ductus arteriosus. Thus, the aortic valve is differentiated from the pulmonary valve by identification of the arteries in which they reside. The entry of the systemic and pulmonary venous channels to the appropriate atria can also be seen. After the basic structure of the heart was established and cardiac normality identified the M-line was then directed through the valve or chamber to be studied.

The pulmonary and aortic valves and the foramen ovale flap were readily visualised directly and the M-line positioned through them. A suitable recording for measuring the ventricular chambers can only be obtained in the four chamber view if the M-line can be located perpendicular to the ventricular septum. This is only possible if the fetus lies with either shoulder towards the transducer. If the fetal position is unsuitable a short axis view of both ventricles should be obtained as seen in Fig. 2. It is then possible to sweep from the atrioventricular valves down into the body of both ventricles to obtain a measurement of the minor axis of both ventricles.

The measurements made included the following.

AORTIC ROOT

The maximum dimension of the aortic root was measured only in an orientation when the aortic valve closure line could be seen as in Fig. 3.

LEFT ATRIAL DIMENSION

The maximum dimension of the left atrium was measured. Since the apparent size of the left atrium is dependent on the orientation of the fetus, left atrial measurements were only made when there was no

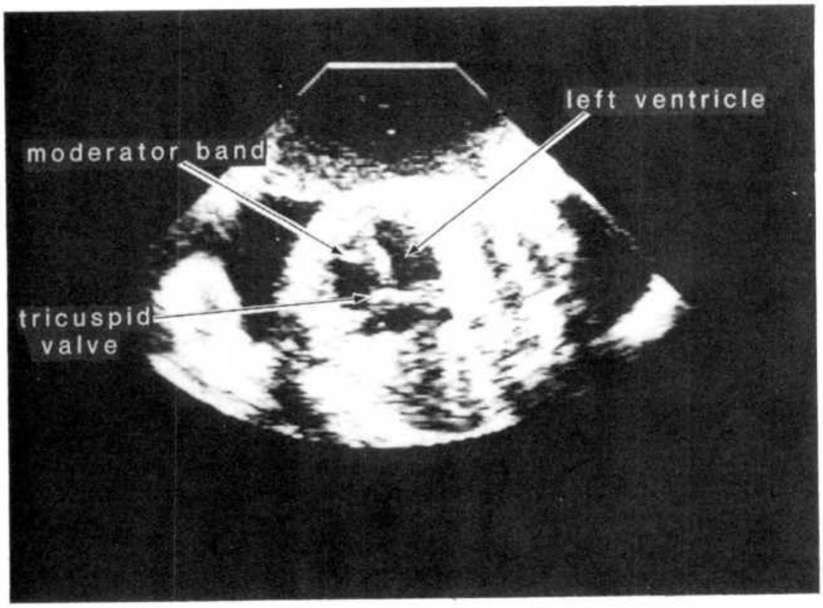

Fig. 1 *A four chamber projection of a normal fetal heart showing increased echoes in the apex of the right ventricle and a more apically inserted atrioventricular valve in this chamber.*

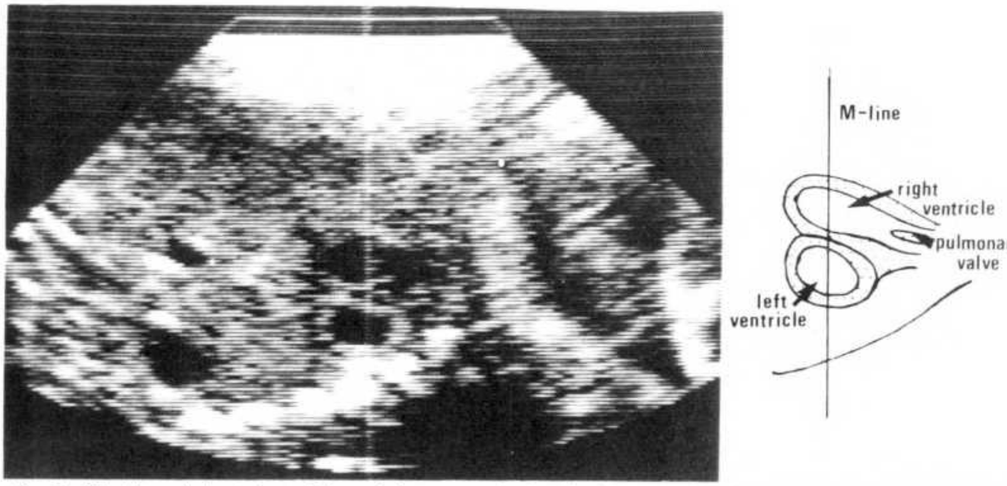

Fig. 2 *The M-mode line is located through the two ventricular chambers seen on a short axis projection. The fetal head lies to the right of the picture, the diaphragm and fetal liver to the left of the fetal heart.*

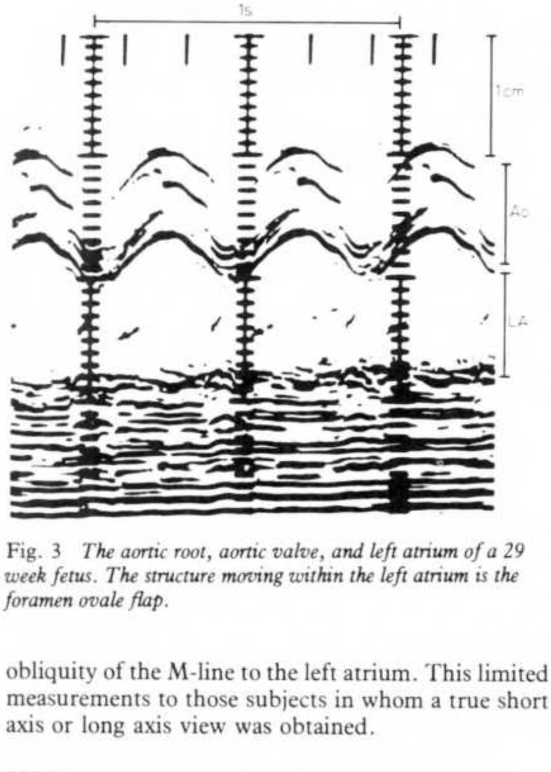

Fig. 3 *The aortic root, aortic valve, and left atrium of a 29 week fetus. The structure moving within the left atrium is the foramen ovale flap.*

obliquity of the M-line to the left atrium. This limited measurements to those subjects in whom a true short axis or long axis view was obtained.

RIGHT AND LEFT VENTRICULAR DIMENSIONS

End-diastolic measurements were made at the maximum ventricular dimension. This is recognised to be a slightly larger dimension than that obtained by timing the measurement to coincide with the R wave of the electrocardiogram. This dimension was chosen because the fetal electrocardiogram was only recorded in 48 of the 200 subjects in whom these measurements were made. Measurements were made between the endocardial surfaces just apical to the recording of the mitral or tricuspid valves. To measure both right and left ventricular dimensions the short axis view was used. In some instances this could not be obtained and the long axis view of the left ventricle was used. This latter view is valid for left ventricular measurements but since the beam crosses only the outlet portion of the right ventricle, right ventricular dimensions were not estimated when only the long axis view was available.

SEPTAL AND POSTERIOR LEFT VENTRICULAR WALL THICKNESS

These measurements were taken from recordings made for ventricular dimension measurement and were made at the same point as that taken for end-diastolic dimension. Fig. 4 shows a suitable recording for measurement of right and left ventricular internal dimensions, and septal and posterior left ventricular wall thickness.

All the measurements were made to the nearest 0·5 mm. No ventricular measurement was made when there was doubt concerning the definition of endocardial surfaces. The results were analysed statistically by regression analysis and 95% confidence limits were derived.

Left and right ventricular ejection times were measured by direct observation of the aortic and pulmonary valves when both opening and closure were adequately visualised.

Results

These are divided into the descriptive echocardiographic data and the measurement data.

DESCRIPTIVE DATA

Arterial valve and foramen ovale flap motion

There are several echocardiographic sections in which the pulmonary or aortic valve may be visualised.[2] Whichever orientation is used to perform the M-mode record the arterial valves appear the same; with a "box" shape in systole and sloping closure line often with what appears to be an "A" dip. Fig. 5 shows the pulmonary valve motion in a 19 week fetus. Below the M-mode trace the combined maternal and fetal electrocardiogram is recorded from midline external abdominal electrodes. Fig. 3 shows the familiar aortic valve "box" appearance in a 29 week fetus with the left atrium lying posteriorly. The echoes within the left atrium were shown on the two dimensional scan to originate from the foramen ovale flap. This has a characteristic biphasic movement throughout each cardiac cycle, seen more clearly in Fig. 6. This pattern of motion was observed in every fetus studied. Closure, or approximation of the foramen ovale flap to the atrial septum, is related to atrial systole. The foramen ovale then opens and closes more gently during ventricular systole. Opening again occurs and the cycle is then repeated with the sharp closure of atrial systole. Left atrial wall motion can also be seen in this recording.

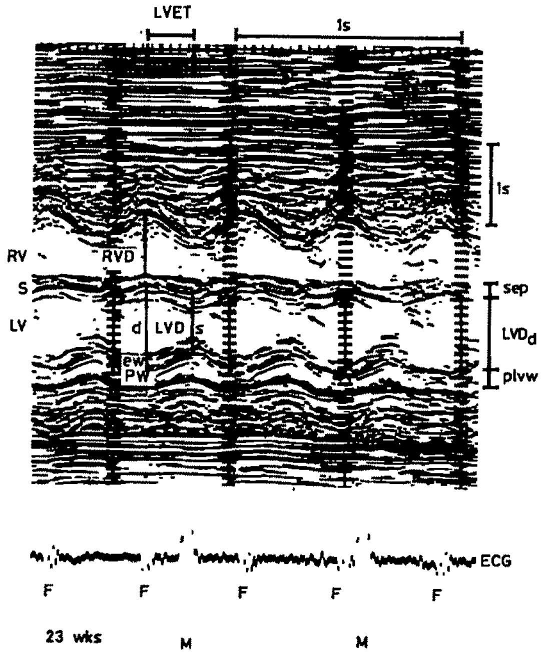

Fig. 4 *A suitable M-mode echocardiogram for measuring right and left ventricular chamber sizes and septal and left ventricular wall thickness.*

Atrioventricular valve and ventricular wall motion

Fig. 7 shows the M-mode echocardiogram sweeping between both atrioventricular valves. The two atrioventricular valves are indistinguishable from each other by their M-mode appearance alone. Differentiation of the atrioventricular valves depends on the two dimensional identification of ventricular morphology as described in the Methods section. Some indication may be gained by looking at right ventricular wall motion which always appears to have a much more undulating pattern than the left ventricular wall in the normal fetus (Fig. 6). In all the fetuses the ventricular septum moved towards the posterior left ventricular wall in systole. In addition, by sweeping up from the atrioventricular valves to the aorta, mitral-aortic continuity and tricuspid-aortic discontinuity can be shown. A mitral-aortic sweep is seen in Fig. 8.

MEASUREMENT DATA

The aortic root could be clearly identified and a measurement was obtained in all 200 subjects. In 54 earlier subjects a measurement of the aortic root was made when the feasibility of adequate M-mode recordings was being assessed and a recording of the aortic root alone was attempted. The additional measurements were included in the statistical data. In 45 subjects both arterial valves were visualised adequately for estimates of both right and left ventricular ejection times to be measured. Estimates for both were similar, being 200 ms with a range of ±40 ms. Since left atrial position depends entirely on the fetal cardiac orientation it was only reliably recorded in 107 of the subjects. The incidence of success in achieving an adequate left atrial measurement did improve, however, as the study progressed.

Adequate recordings for both left and right ventricular dimensions were achieved in 167 of the 200 subjects, with fewer failures in the latter part of the study. In a further eight subjects the septal thickness, left ventricular internal dimension, and posterior left ventricular wall thickness could be measured in a long axis view of the left ventricle, but no right ventricular measurement could be made. In a further three subjects the septal endocardial surfaces were visualised but not the posterior left ventricular wall; thus, in a total of 178 subjects septal thickness was measured.

Regression analysis showed that the best correlation for each measurement to gestational age was a straight line of the form $y=m\,x+b$. With some measurements there was an indication of a deviation from linearity in the later weeks of pregnancy but this was small,

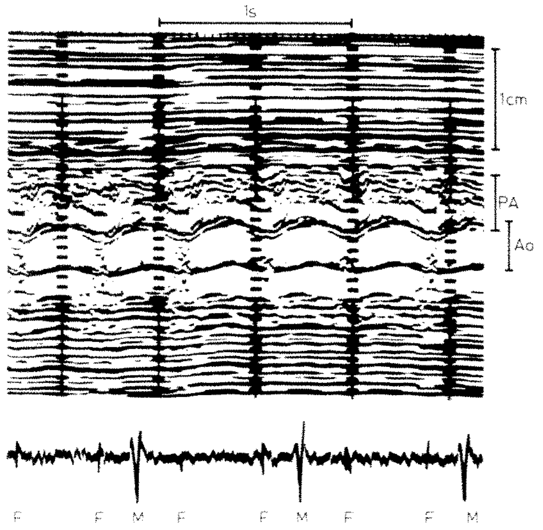

Fig. 5 *M-mode echocardiogram of the pulmonary valve motion in a 19 week fetus. The fetal electrocardiogram is also shown. Fetal complexes are marked F, maternal M.*

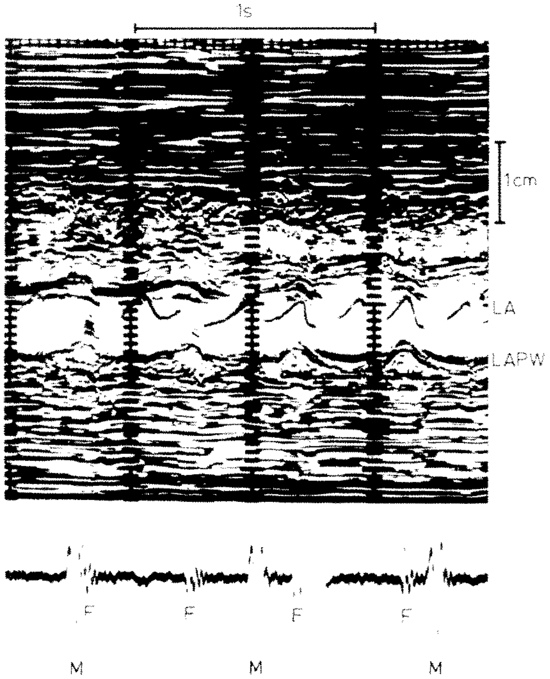

Fig. 6 *Left atrial wall motion, and foramen ovale flap motion in a 22 week fetus. The foramen ovale flap moves away from the atrial septum twice within each cardiac cycle.*

inconsistent, and based on few data points. The "flared" 95% confidence limits for individual measurements (Table) were only slightly wider at the extremes of the range than at the mean gestation; this again argues against a significant deviation from linearity. Straight 95% confidence limits defined by twice the standard error of the estimate of y (SEE y×2) were in close agreement with the "flared" limits and were entirely adequate for practical purposes.

Fig. 9, 10, 11, 12, 13, and 14 show, respectively, the relation of septal thickness, posterior left ventricular wall thickness, the internal dimension of the aortic root, right ventricular internal dimension, left ventricular internal dimension, and left atrial internal dimension to gestational age. The correlation coefficients (r) ranged from 0·836 to 0·895 and these were statistically highly significant ($t > 14·968$; $p < 0·001$). Statistical data for the relation of each measurement to gestational age and the equations for the lines are given with the appropriate figure.

Discussion

Realtime imaging of the fetal cardiac anatomy has been described by several authors.[1 2 4] Prenatal detection of structural cardiac abnormalities has also been reported during the middle[5 6] and last trimesters[4] of pregnancy. Others have reported that the M-mode echocardiogram can also be obtained in fetal life.[4 7 8] We have described the normal appearance of the complete M-mode echocardiogram during fetal life and the method of obtaining it.

The M-mode echocardiogram provides complementary information to the two dimensional study. For this to be of value and to avoid errors in interpretation, it must be performed in a standard way such as that we have described. The M-line must be positioned by accurate two dimensional guidance and constant reference between the M-mode and the two dimensional image must be made as chamber orienta-

Table *95% confidence limits for measurements at 16 weeks, 39 weeks, and at mean gestational age*

	SEE y×2	*16 weeks*	*Mean gestation*	*39 weeks*
Septal thickness	0·088	0·0873	0·0867	0·089
Posterior left ventricular wall thickness	0·066	0·067	0·066	0·067
Aortic root	0·138	0·138	0·137	0·139 (38)
Right ventricular internal dimension	0·306	0·306	0·304	0·311
Left ventricular internal dimension	0·300	0·300	0·298	0·304
Left atrial internal dimension	0·2995	0·2969 (17)	0·297	0·307

Note: Confidence limits were not found to "flare" significantly at the extremes of gestational age.

tion to the transducer may change during fetal movement. This is particularly so in the very active mid-trimester fetus.

The M-mode echocardiogram can demonstrate that cardiac structures have a characteristic pattern of motion. It can show actual cusp separation of valve leaflets where the two dimensional image may only show a moving valve which could be atretic. It can show the "box" shape in systole and sloping central closure line characteristic of both normal arterial valves. In the normal individual in postnatal life it is possible to distinguish the aortic from the pulmonary valve by their patterns of motion and by their systolic time intervals. In contrast, in the normal fetus this is not possible. The motion of both valves is indistinguishable and ejection times were similar for both aortic and pulmonary valves. Since the speed of the recordings was 50 mm/s minor differences cannot be excluded. Recording at faster speeds, however, provided tracings that were inadequate for interpretation. Notwithstanding this reservation it appears reasonable that aortic and pulmonary systolic time intervals should be similar, since both right and left ventricles are ejecting against similar resistances.

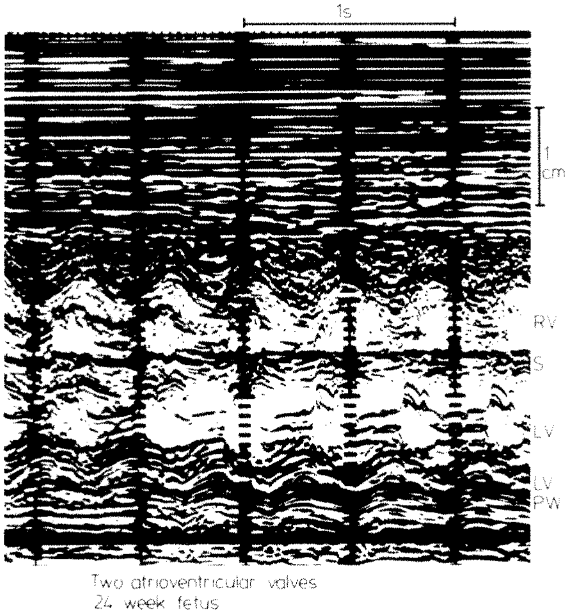

Fig. 7 *A "sweep" between the two atrioventricular valves of each ventricle in a 24 week fetus. The tricuspid valve motion is seen opening within the right ventricle, the mitral valve within the left ventricle.*

Similarly, the two atrioventricular valves are indistinguishable by M-mode alone and must be identified from their respective chamber. The pattern of their motion is the "M" shape seen mainly in the mitral valve in postnatal life. Septal motion is always towards the left ventricular wall in systole. Other authors[3] have suggested a high incidence of paradoxical septal motion in fetal life. We have never seen this, however, in a normal fetal heart. Before 20 weeks gestation septal motion is flat but after this time it has the appearance seen in Fig. 8.

The pattern of motion of the foramen ovale flap can be observed on M-mode. On the two dimensional scan it could be seen to move throughout the cardiac cycle but when recorded in M-mode this motion could

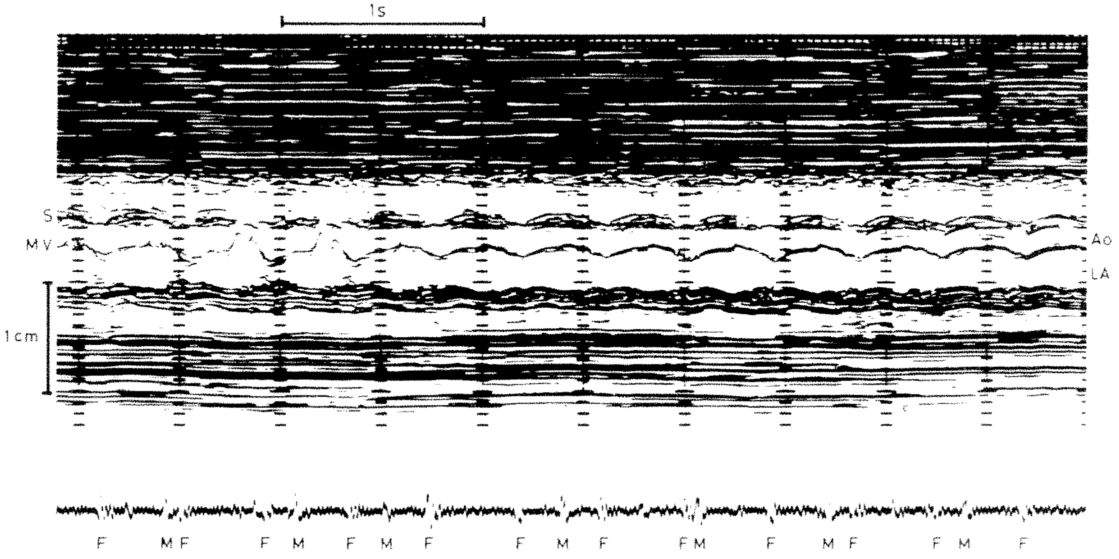

Fig. 8 *This shows a mitral-aortic sweep and shows mitral-aortic and septal-aortic continuity.*

be seen to be organised. The flap approximates to the atrial septum, or closes, twice during each cardiac cycle (Fig. 4). This movement pattern is consistently recordable in every normal fetal heart. When this motion was timed with the fetal electrocardiogram and left atrial wall motion there appeared to be an abrupt closure of the foramen ovale flap during atrial systole; it then opened more gradually and then drifted closed during ventricular systole. Closure during ventricular systole may be the result of the effect

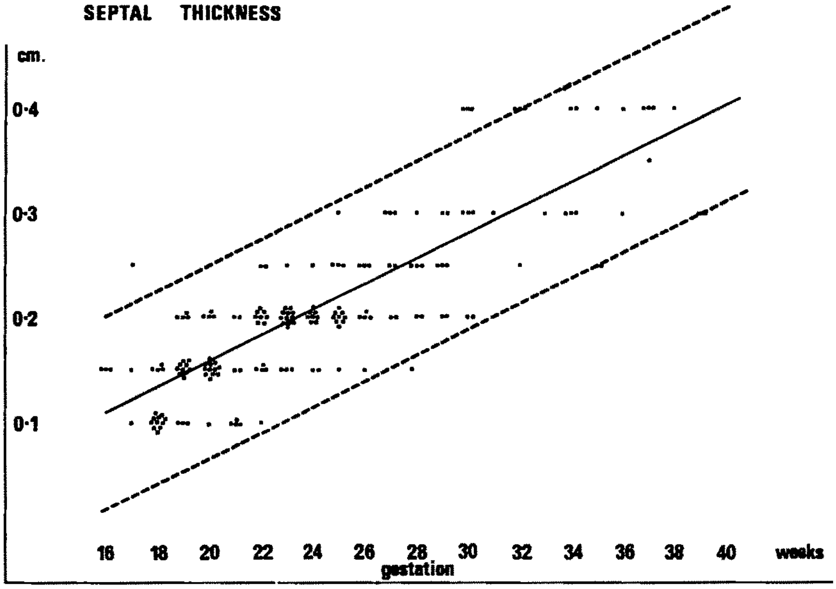

Fig. 9 *Septal thickness plotted against gestational age (n=178). The 95% confidence limits represent twice the standard error of the mean in each graph.* $Y=0{\cdot}012\times-0{\cdot}088$, $r=0{\cdot}836$, $t=20{\cdot}183$, $p<0{\cdot}001$, *SEE* $y\times2=0{\cdot}088$.

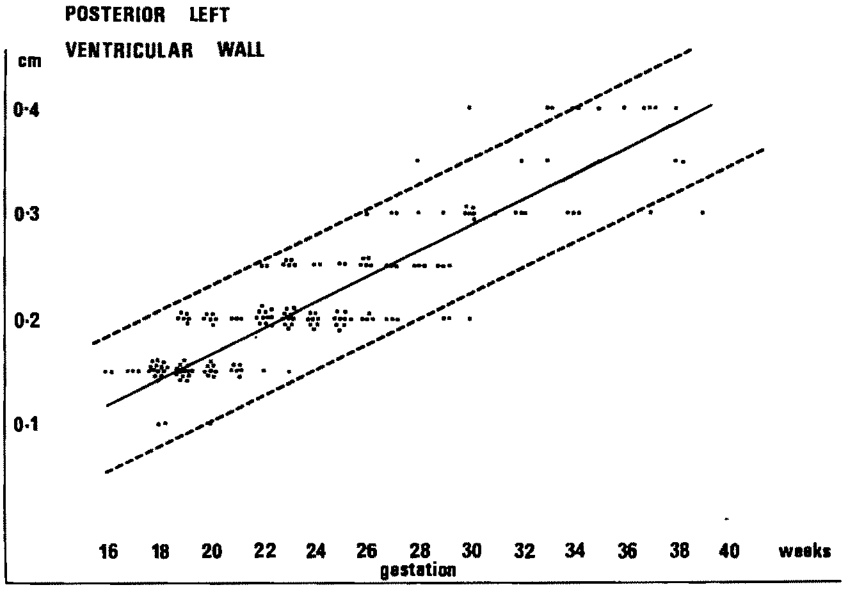

Fig. 10 *Posterior left ventricular wall thickness plotted against gestational age (n=175).* $Y=0{\cdot}012\times-0{\cdot}063$, $r=0{\cdot}884$, $t=24{\cdot}929$, $p<0{\cdot}001$, *SEE* $y\times2=0{\cdot}66$.

of the pulmonary venous return to the left atrium, small though it may be, meeting a closed mitral valve. Once ventricular systole ends the foramen ovale flap opens again. This suggests a biphasic pattern of flow from the right to the left atrium related in part to atrial systole but also being determined by the relative systemic and pulmonary venous returns. The factors that produce this sequence are at present speculative and merit further study.

From the growth charts it can be seen that septal and left ventricular wall thickness grow in a parallel fashion throughout pregnancy, increasing between three and fourfold during gestation. The left and right ventricular dimensions again parallel each other until

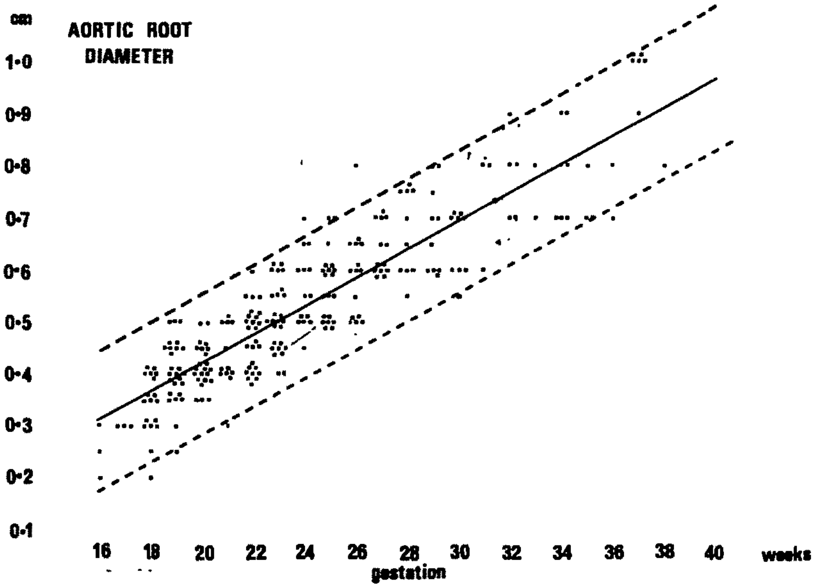

Fig. 11 *Aortic root diameter plotted against gestational age* ($n=254$). $Y=0{\cdot}028\times-0{\cdot}136$, $r=0{\cdot}895$, $t=31{\cdot}925$, $p<0{\cdot}001$, SEE $y\times2=0{\cdot}138$.

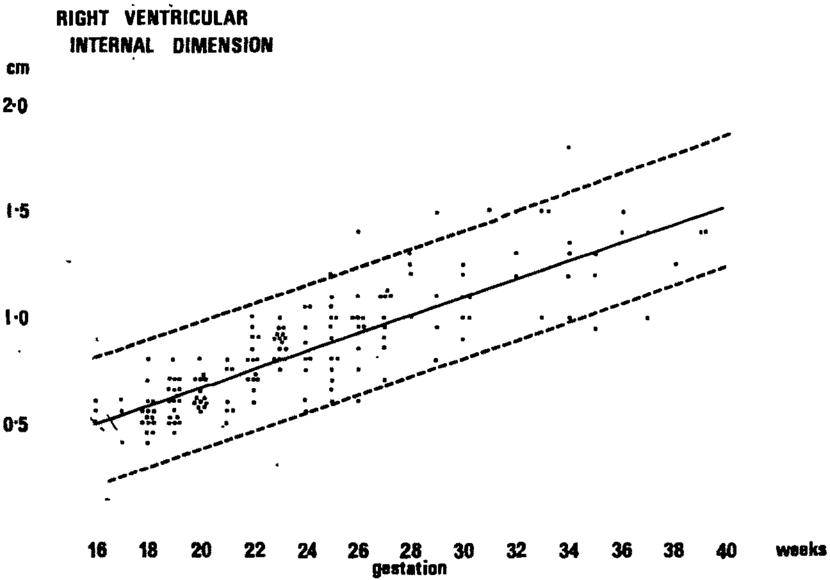

Fig. 12 *Right ventricular internal dimension plotted against gestational age* ($n=167$). $Y=0{\cdot}045\times-0{\cdot}228$, $r=0{\cdot}844$, $t=20{\cdot}183$, $p<0{\cdot}001$, SEE $y\times2=0{\cdot}306$.

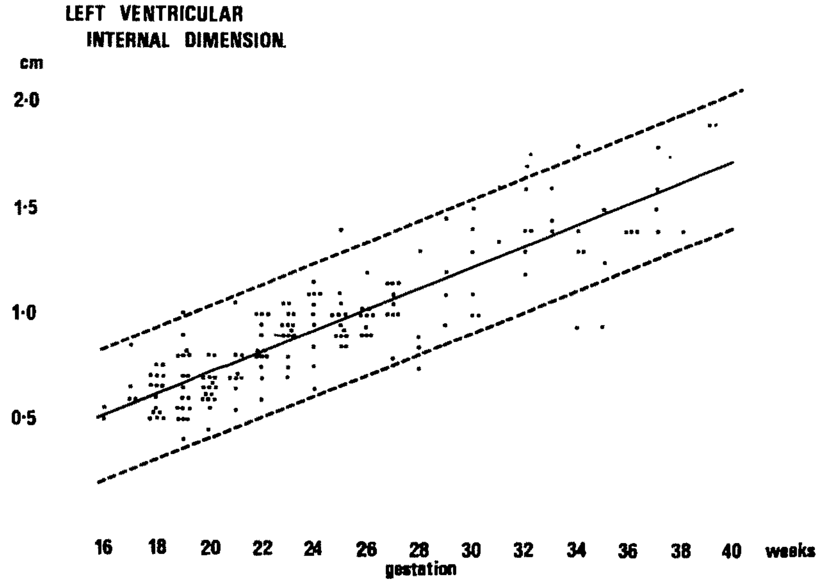

Fig. 13 *Left ventricular internal dimension plotted against gestational age* ($n=175$). $Y=0{\cdot}049\times-0{\cdot}262$, $r=0{\cdot}876$, $t=23{\cdot}944$, $p<0{\cdot}001$, SEE $y\times2=0{\cdot}3$.

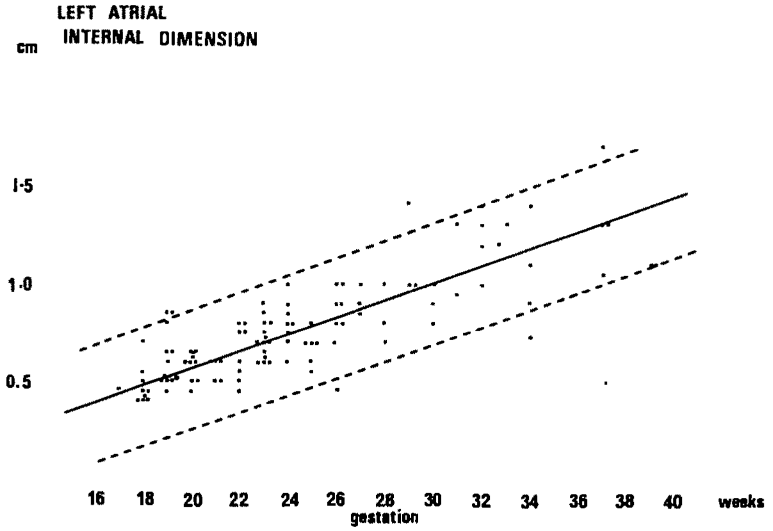

Fig. 14 *Left atrial internal dimension plotted against gestational age* ($n=107$). $Y=0{\cdot}040\times-0{\cdot}214$, $r=0{\cdot}823$, $t=14{\cdot}968$, $p<0{\cdot}001$, SEE $y\times2=0{\cdot}296$.

term, bearing approximately a one to one relation to each other throughout gestation. Again this may represent equal pressure within the two chambers and equal volumes handled by each chamber. The mean internal diameter of each at 16 weeks gestation is about 0·5 cm, increasing to a mean of approximately 1·5 cm at term. The left ventricular dimension at term compares well with published neonatal left ventricular dimensions.[9] It should be noted, however, that our left ventricular internal dimension is not strictly end-diastolic as has been explained in the text but is fractionally larger as it represents the maximum internal dimension. The left atrial and aortic root dimensions also show similar growth patterns, but it is interesting that the ratio of left atrial to aortic root dimension is consistently greater than unity, being approximately

1·5:1. Since the fetal aortic root dimensions at term are similar to those of newborn infants, this suggests that in the fetus the left atrium is enlarged compared with postnatal life. Examination of Fig. 15 perhaps explains this fact because it can be seen that the Eustachian valve is almost completely preventing the passage of inferior vena caval blood through the tricuspid valve; instead the flow is mainly directed through the foramen ovale into the left atrium. The inferior vena cava in fetal life carries all the venous flow from the lower half of the body and also the venous return from the placenta. These anatomical and functional features of the fetal heart have been well described in animal specimens, especially in lambs. Some observers of the fetal lamb suggest that left ventricular output is greater than the right[10] though others find similar outputs from each ventricle.[11]

The relative left atrial enlargement that has been observed in these normal human fetuses suggests that left atrial flow is high. This supports the concept that left ventricular output may be greater than that of the right ventricle. This is, however, in conflict with the data indicating similar right and left ventricular dimensions and similar aortic and pulmonary valve systolic time intervals. Thus, further studies of the normal human fetus are required to elucidate the normal fetal haemodynamics.

In all the measurement data the best fit correlation between dimensions and gestational age was a straight line. Inability to detect a curvilinear relation may be because we are observing growth at its most rapid phase. It may be, however, that when more data have been accumulated in older fetuses the growth charts may need modification, but at present they give a good indication of normal dimensions and as such should be clinically useful.

Dimensional data obtained from normal fetuses should be valuable in the interpretation of abnormalities of the fetal heart. For example, if the right ventricle is larger than the left it is useful to know whether the right ventricle is dilated or the left ventricle is small for the gestational age. A single measurement out of step with the others, however, might lead one to suspect a structural cardiac abnormality. The growth charts shown here should not be used for gestational age dating as this is more accurately achieved by other means. They may, however, be useful in the more detailed study of the effects of growth retardation on the heart. In such cases all the measured variables might be expected to show a similar shift to the left.

In summary, familiarity with the appearance of the normal M-mode echocardiogram and the growth of cardiac structures in the normal fetus should help in

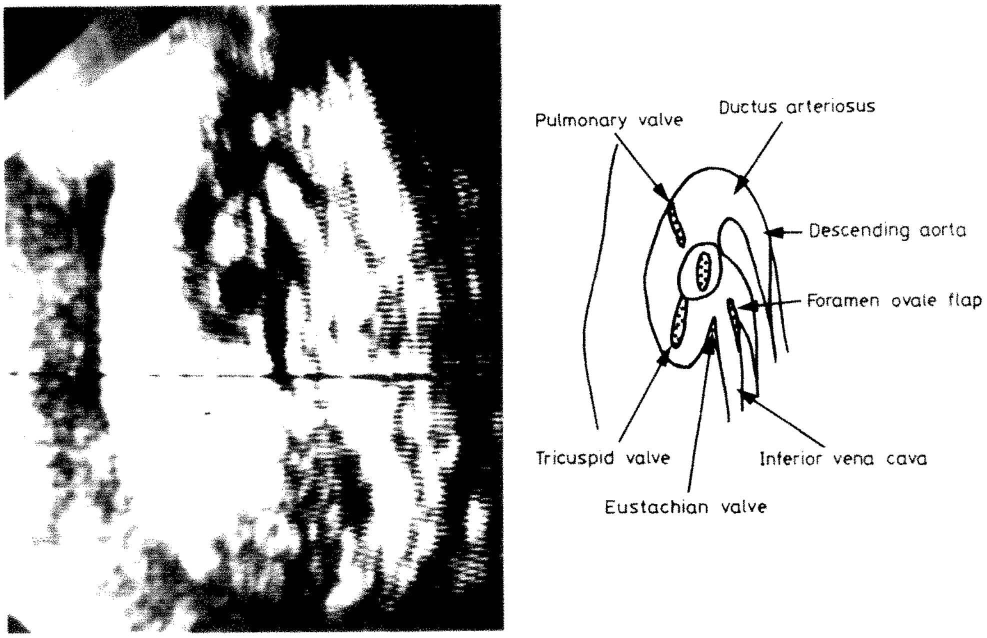

Fig. 15 *The fetal heart is visualised in the ductal plane. The aortic valve is seen in the centre. The inferior vena cava can be seen entering the right atrium but the Eustachian valve and the foramen ovale flap can be seen to direct most of the flow to the left atrium.*

the elucidation of structural cardiac abnormalities in fetal life. Further study should aid understanding of cardiac function in the normal human fetus.

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Cardiac dimensions and myocardial function of infants with congenital hypothyroidism

An echocardiographic study

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SUMMARY This study was undertaken to evaluate the cardiac dimensions and various indices of myocardial function, determined by echocardiography, in a group of 12 infants with congenital hypothyroidism. Left ventricular systolic and diastolic dimensions, posterior wall thickness, end-diastolic and systolic volumes were all significantly lower in the hypothyroid infants compared with 25 normal infants of the same age. No pericardial effusion was found. Hypothyroid infants had a lower heart rate with a reduced cardiac output. The mean velocity of circumferential fibre shortening and the shortening fraction of the left ventricle were normal. The pre-ejection period of the left ventricle (PEP), however, was abnormally prolonged as well as the ratio PEP over left ventricular ejection time (PEP/ET). This ratio correlated inversely with the end-diastolic volume, suggesting that the increased PEP/ET could be partly the result of decreased preload.

Several screening programmes have indicated that congenital hypothyroidism can be successfully detected during the first weeks of life, preventing irreversible cerebral damage.[1] To our knowledge, no data are available concerning the cardiac size and myocardial function of these infants. Because of the structural and functional differences between neonatal and adult myocardial tissue,[2 3] extrapolations from studies carried out in adults[4] or older children[5] must be made with great caution. Furthermore, the possibility that early diagnosis and treatment could minimise myocardial involvement and be an added benefit to the screening programme deserved investigation. We wish to report the cardiac dimensions and various indices of myocardial function, determined by echocardiography, in a group of newborn infants with congenital hypothyroidism. For comparison, the same echocardiographic study was performed on 25 normal infants of the same age.

Subjects and methods

The procedure according to which patients are screened and recalled in the Quebec screening programme for neonatal hypothyroidism has previously been described.[6 7] Twelve infants aged 3 to 9 weeks (mean age 5·4 weeks) detected by this network were included in the study. The study procedure, applied to all patients on the day of the first visit, has also been published[7] and includes the establishment of a clinical hypothyroid index (Table 1), chest and lower limbs *x*-rays (to evaluate the surface area of distal femoral ossification centres), and analysis of plasma T3, T4, and TSH. To this routine evaluation was added the recording of an echocardiogram.

Echocardiograms were recorded on an Ekoline model 20A ultrasonoscope interfaced with a Honeywell Cambridge fibreoptic recorder. An electrocardiogram with a well-defined Q wave was simultaneously recorded. A 5 MHz unfocused transducer was used in all patients. The following left ventricular systolic time intervals were measured[8]: the pre-ejection period (PEP) from the onset of the QRS complex to the opening of the aortic valve; the ejection time (ET) from the opening to closure of aortic valves; and the ratio PEP/ET. Posterior wall and septal thickness in diastole, and systolic (LVIDs) and diastolic (LVIDd) internal dimensions of the left ventricular cavity were also measured. These measurements were made according to the recommendations of the American Society of Echocardiography.[9] From the left ventricular internal dimensions, the following indices

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Table 1 *Clinical signs and symptoms used for the hypothyroid clinical index score (for details see Reference 6)*

Hernia
Feeding problems
Hypotonia
Constipation
Tongue
Inactivity
Skin mottling
Dry skin
Fontanelle post. <0·5 cm
Typical facies

Table 2 *Clinical, radiological, and biochemical characteristics of hypothyroid patients*

	No of patients	*Mean*	*SD*
Clinical index*	12	8·1	3·2
T4 (ng/dl)*	12	1·8	1·74
T3 (μg/dl)*	10	81	43
TSH (μU/ml)*	12	468	261
Bone maturation delay (wk)			
Distal femoral	12	9·34	2·62
Proximal tibial	12	10·37	2·25

*Normal values.[6] Clinical index: 0·6±0·1, T4 (plasma thyroxine): 5–14 ng/dl, T3 (plasma triiodothyronine): 70–220 μg/dl, TSH (thyrotropin-stimulating hormone): less than 20 μU/ml.
Abbreviation: SD, one standard deviation.

Table 3 *Comparison between ventricular dimensions of hypothyroid patients and control group*

	Hypothyroid		*Control*		*p*
	Mean	*SD*	*Mean*	*SD*	
LVIDd (mm)	19	2	20	2	<0·05
LVIDs (mm)	13	2	14	2	<0·05
EDV (cm³)	7·1	2·1	8·7	2·5	<0·1
ESV (cm³)	2·3	0·9	3·1	1·1	<0·05
LVPWd (mm)	2·9	0·34	3·3	0·48	<0·05
IVSDd (mm)	3·5	0·9	3·4	0·5	NS

Abbreviations: LVIDd, left ventricular internal diameter in diastole; LVIDs, left ventricular internal diameter in systole; EDV, end-diastolic volume; ESV, end-systolic volume; LVPWd, left ventricular posterior wall thickness in diastole; IVSDd, interventricular septal dimension in diastole.

were calculated: the shortening fraction of the LV ($SF=LVIDd-LVIDs/LVIDd$), and mean velocity of circumferential fibre shortening (mean $VCF=(LVIDd-LVIDs)/(LVIDd\times ET)$), expressed in circumferences per second. Systolic and diastolic volumes of the left ventricle were calculated according to the cube formula,[10] allowing evaluation of cardiac output and stroke volume. All measurements were made to the nearest 5 ms at a paper speed of 100 mm/s. In all patients, at least five different measurements were made for each value. In order to establish a control group, the same echocardiographic study was carried out in 25 normal infants aged 4 to 8 weeks. In this group, ejection time but not pre-ejection period strongly correlated with heart rate ($r=-0{\cdot}76$). The difference between the ejection time observed in the hypothyroid group and that predicted by the regression equation calculated from our normal data for the appropriate heart rate was expressed as the change in this interval in milliseconds (Δ ET). (Predicted $LVET=331{\cdot}4-0{\cdot}933$ HR, $p<0{\cdot}05$.)

Statistical comparison between the echocardiographic data of the hypothyroid patients and that of the normal group was made by unpaired t test. Regression analysis was utilised to evaluate the correlations between the indices of myocardial function which were altered and the clinical index and the thyroid funtion tests. Normal biochemical values for thyroid function have already been published.[6]

Results

THYROID FUNCTION

Clinical, radiological, and biochemical data for the 12 patients are summarised in Table 2.

CARDIAC DIMENSIONS

Echocardiographic measurements of the minor axis of the left ventricle and the volumes calculated for the hypothyroid and the normal groups are shown in Table 3. Ventricular systolic and diastolic echocardiographic dimensions of hypothyroid patients were significantly lower than those of the normal group ($p<0{\cdot}05$). This was also true for ventricular volumes and left posterior wall thickness. No difference was found for septal thickness. No patient had echocardiographic evidence of pericardial effusion.

MYOCARDIAL PERFORMANCE

Mean velocity of circumferential fibre shortening (mean VCF) as well as shortening fraction and stroke volume of the hypothyroid infants were normal (Table 4). The pre-ejection period, however, was prolonged ($p<0{\cdot}02$) as well as the ratio PEP/ET ($p<0{\cdot}001$). The ejection time measured was consistently shorter than that predicted for the appropriate heart rate (average Δ ET of 24 ms). Heart rate was also significantly lower ($p<0{\cdot}001$) and cardiac output was decreased when compared with normal ($p<0{\cdot}02$) (Table 4).

CORRELATION STUDIES

The correlation coefficients between abnormal echocardiographic variables and biological data are shown in Table 5. The clinical index of hypothyroidism was the only variable which correlated not only with systolic time intervals but also with ventricular

Table 4 *Comparison between myocardial performance of hypothyroid patients and control group*

	Hypothyroid (No.12)		*Control (No.25)*		*p*
	Mean	*SD*	*Mean*	*SD*	
Heart rate	132	19	153	16	0·001
SF	0·31	0·08	0·30	0·06	NS
Mean VCF (circ/s)	1·69	0·42	1·6	0·36	NS
PEP (ms)	66	11	57	7	0·02
PEP/ET	0·36	0·06	0·31	0·02	0·001
CO (l/min)	0·63	0·27	0·87	0·26	0·02
EF	0·66	0·11	0·64	0·09	NS
SV (ml)	4·8	1·8	5·6	1·8	NS

Abbreviations: SD, one standard deviation; SF, shortening fraction of the left ventricle; mean VCF, mean velocity of circumferential fibre shortening; PEP, pre-ejection period; ET, ejection time; CO, cardiac output; EF, ejection fraction; SV, stroke volume; NS, not significant.

Table 5 *Correlation coefficients between echocardiographic variables, plasma T4, T3, and clinical index at time of diagnosis*

Variables	*T4*	*T3*	*Index*
Heart rate	0·34	0·21	−0·57
PEP	−0·52	−0·49	0·59
PEP/ET	−0·65	−0·71	0·57
LVIDd	0·41	0·39	−0·62
LVIDs	0·14	0·41	−0·59
LVPWd	−0·34	−0·54	0·76
EDV	0·40	0·32	−0·57
ESV	0·19	0·51	−0·60
CO	0·54	0·35	−0·58

Abbreviations: as in Tables 3 and 4.
A positive or negative coefficient of 0·58 is significant at a p value of 0·05.

dimensions and cardiac output. There was also a significant correlation between the thyroid hormone plasma levels and the PEP/ET ratio.

Discussion

Severe hypothyroidism has long been known to produce abnormalities of cardiac structure and function in adults and children. In typical cases the myocardium is oedematous and basophilic with accumulation of mucopolysaccharides disrupting myocardial integrity.[11 12] Clinically, bradycardia, reduced cardiac output,[13] pericardial effusion,[14] cardiomegaly, and dimished myocardial contractility[15–17] are classical features. The effect, however, of decreased thyroid activity *in utero* on the cardiovascular condition of the newborn has never been specifically studied. Since the placenta is not permeable to TSH and T4, the fetus is completely autonomous as far as the hypothalamic-pituitary-thyroid axis is concerned. Recent studies have suggested that this system is functionally mature at the end of the last trimester of gestation (phase III of fetal thyroid-system ontogenesis).[18] To assess the influence of lack of thyroid hormone on the circulatory sytem during the first weeks of life, a non-invasive approach has been adopted in this study. The validity of echocardiography for myocardial function study and ventricular cavity measurements is now well established.[19]

Infants in this study had left ventricular cavities smaller than normal with no echocardiographic evidence of pericardial effusion. This finding is particularly significant in the presence of bradycardia that normally would tend to increase the end-diastolic volume. This suggests that the drop in the cardiac output and of the venous return is severe enough to counterbalance the increase in diastolic filling caused by lowering of the heart rate.

Results of myocardial function study of our hypothyroid patients seem to be contradictory. On one hand, PEP and PEP/ET have been found abnormally prolonged. This has been a consistent finding in all previous studies on hypothyroidism and interpreted as a sign of decreased myocardial contractility.[16 17 20] On the other hand, the ejection phase indices of ventricular performance such as mean VCF and shortening fraction were both within normal limits. This apparent contradiction can perhaps be explained by the fact that systolic time intervals (PEP, PEP/ET) are influenced not only by intrinsic myocardial contractility but also by changes in preload and/or afterload of the ventricles.[21] In this study, cardiac output has been reduced. It has previously been shown that this low blood flow is essentially the result of the depressed metabolic requirements of the body.[13 22] A low cardiac output is necessarily associated with a fall in the venous return to the heart and consequently a decrease in the preload of the ventricle. This decrease in preload could, at least partly, explain the lengthening of the pre-ejection period and the abnormal PEP/ET ratio which were observed in our group of patients. To verify this hypothesis, we have studied the correlation betwen the PEP/ET ratio and the diastolic volume of the left ventricle, which is a reliable reflection of its preload. Though the number of patients is too small to allow any definitive conclusion, the results presented in the Figure show that left ventricular volume is inversely related to PEP/ET ratio. A completely different situation would be observed in primary myocardial dysfunction, where the pre-ejection period would indeed be prolonged but the cardiac chambers would also be enlarged. In contrast to the PEP/ET ratios, VCF and the shortening fraction are relatively unaffected by either an acute,[23] or chronic[24] alteration of the preload.

Definite signs of myocardial dysfunction are therefore not present in the hypothyroid neonate. This may be because of the different structural and functional characteristics of the neonatal myocardium.

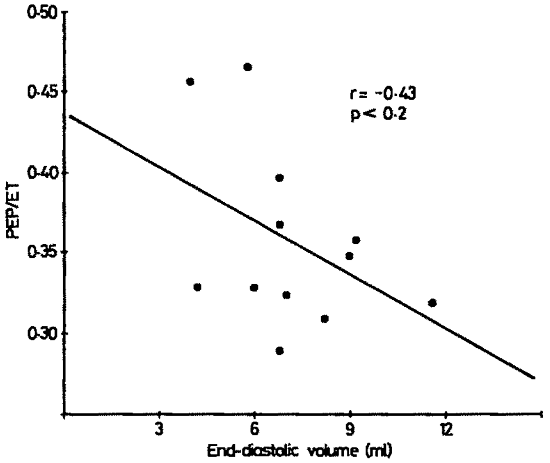

Fig. *Relation between left ventricular pre-ejection period (PEP)/left ventricular ejection time (ET) and left ventricular end-diastolic volume (expressed in ml).*

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Familial hypertrophic cardiomyopathy: vectorcardiographic findings in echocardiographically unaffected relatives

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SUMMARY The electrocardiographic and vectorcardiographic (Frank system) features of the first degree relatives of subjects with documented familial hypertrophic cardiomyopathy were analysed. A total of nine affected members and 29 relatives were examined in four families. The subjects were considered to be affected when the septal to free posterior wall thickness ratio exceeded 1·3 at M-mode echocardiography.

Four relatives had asymmetric septal hypertrophy. Among 25 relatives without evidence of asymmetric septal hypertrophy, two over 20 years and 10 under 20 years of age showed increased voltage of QRS anterior forces (Q_z amplitude greater than 0·80 mV) on the orthogonal electrocardiogram. The vectorcardiographic data of the relatives under 20 years of age without evidence of asymmetric septal hypertrophy (18 subjects) were compared with those of 38 normal control subjects of comparable age range. The young relatives without disproportionate septal hypertrophy had significantly greater Q_z amplitude and Q/R_z ratio than the normal control subjects. In contrast, the echocardiographic data were not significantly different.

We suggest that the electrocardiographic finding of abnormal anterior forces in one or more first degree relatives of subjects with documented hypertrophic cardiomyopathy may constitute a valuable aid in ascertaining the genetic transmission of the disease and in recognising affected members without echocardiographic evidence of hypertrophic cardiomyopathy.

Most investigators agree that in some cases hypertrophic cardiomyopathy is genetically transmitted.[1-3] This view has been drawn mainly from echocardiographic studies on the first degree relatives of subjects with documented hypertrophic cardiomyopathy.[1 2 4] In these studies asymmetric septal hypertrophy was used as the diagnostic marker of the disease.[1 4] Several authors, however, have recently questioned the reliability of M-mode echocardiography alone in making the diagnosis.[5-10] Goodwin,[11] for example, emphasised that a firm diagnosis of hypertrophic cardiomyopathy should rely on all clinical and laboratory data, including the history, clinical signs, electrocardiogram, cardiac catheterisation, angiography, and M-mode or two dimensional echocardiography. Furthermore, a positive family study may strongly support the diagnosis of genetically transmitted hypertrophic cardiomyopathy in a propositus with asymmetric septal hypertrophy.[3-11]

The electrocardiogram and vectorcardiogram have commonly been considered secondary aids in the identification or assessment of the severity of hypertrophic cardiomyopathy because they do not show specific abnormalities.[12-21] Consequently, until now little attention has been focused on the electrocardiographic findings in the relatives of subjects with the disease.[2]

In this study we report the electrocardiographic and vectorcardiographic findings in first degree relatives of subjects with documented familial hypertrophic cardiomyopathy, and their relation with M-mode echocardiographic data.

Subjects and methods

Four families were studied, in which two of more living first degree relatives had previous haemodynamic and angiographic evidence of hyper-

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trophic cardiomyopathy. Sudden deaths had occurred in one or more members of three families. All of the surviving members with previously documented hypertrophic cardiomyopathy (index cases) and their first degree relatives (parents, children, brothers, and sisters) were asked to co-operate in the study, which included a history, physical examination, standard 12 lead electrocardiograms, vectorcardiograms, and M-mode echocardiograms. Whenever possible, detailed information on the family members who had died or who did not co-operate (seven subjects) was collected.

Nine index cases (five male and four female, age range from 10 to 61 years, mean 40·2±17·3) and 29 first degree relatives (15 male and 14 female, aged from 4 to 59 years, mean 15·7±11·1) were examined. Of the first degree relatives, eight (two men and six women) were over 20 years and 21 (13 male and eight female subjects, aged from 4 to 20, mean 11·0±6·3) were under 20 years of age. The number of members examined for each family was as follows: family A, two index, three relatives; family B, two index, 10 relatives; family C, three index, 11 relatives; family D, two index, five relatives. The 38 control subjects were under 20 years (18 male and 20 female) without any clinical evidence of cardiovascular disease, and these were compared with those relatives who were younger than 20 years. Their ages ranged from 4 to 20 years, mean 9·9±5·5.

M-MODE ECHOCARDIOGRAPHY

M-mode echocardiograms were recorded using a 2·25 MHz transducer of 1·5 cm diameter and 7·5 cm focal length connected to a modified Smith-Kline Echoline 20A. The output was displayed on a Cambridge strip-chart recorder. The paper speed was 50 mm/s. The examination was performed with the subject in a supine or left semilateral position, via the third or the fourth left intercostal space at the left sternal border.

The following echocardiographic measurements were obtained (Fig. 1).[22] (1) The thickness of the interventricular septum, measured in diastole, at the first deflection of the QRS complex below the tips of the mitral valve leaflets using the leading edge method. (2) The left ventricular posterior wall thickness, measured at the level of the tips of the mitral valve during the same phase of cardiac cycle. (3) The left ventricular end-diastolic internal dimension, measured below the tips of the mitral valve leaflets at the peak of the onset of the R wave. The septal thickness and left ventricular internal dimension were corrected by body surface. The degree of approximation

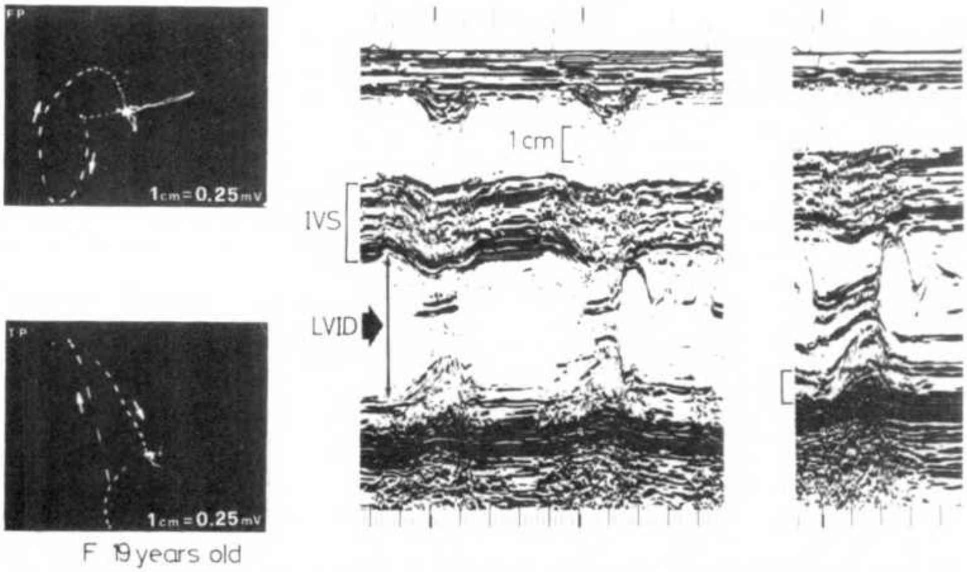

Fig. 1 *The echocardiogram and vectorcardiogram of a 19-year-old woman with angiographically documented diagnosis of obstructive hypertrophic cardiomyopathy. Asymmetric septal hypertrophy is present on the M-mode echocardiogram. The vectorcardiogram shows an anteriorly displaced and rightward oriented QRS loop. IVS, interventricular septum; LVID, left ventricular end-diastolic interval dimension.*

of the anterior mitral valve leaflet to the ventricular septum, prominent systolic anterior movement of the mitral valve, and mid-systolic closure of the aortic valve were assessed.

Measurements of at least three cycles were averaged and separately measured by two investigators. When significant differences were present between the two observers, the final measurement was subjected to arbitration by a third.

Subjects were considered to have asymmetric septal hypertrophy when the septal to free posterior wall ratio was equal to or greater than 1·3. The interventricular septum thickness and end-diastolic left ventricular internal dimension were considered abnormal when they exceeded the normal corrected values.[23]

VECTORCARDIOGRAPHY

Vectorcardiograms were recorded using the Frank lead system with a 1507A Hewlett-Packard Vector Programmer, a Sanborn 760-6A VisoScope, and photographed with a Model 197A Option 05 Oscilloscope Camera. The records were obtained with the subject in the supine position. The thoracic electrodes were placed at the level of the fourth intercostal space. Orthogonal leads were recorded at a sweep speed of 250 mm/s. Frontal, transverse, and left sagittal planes were recorded in each subject. The loops were interrupted so that each dash represented 2·5 ms. Standard notations were used for the localisation of vectors.

The following vectorcardiographic variables were considered: (1) QRS duration; (2) QRS rotation in each plane; (3) Q, R, and S amplitude in x, y, and z; (4) Q/R ratio in z (anteroposterior forces ratio); R/S ratio in x (leftward-rightward forces ratio); (5) voltage and orientation of the QRS maximum vector in frontal and transverse plane; (6) voltage of the maximum leftward spatial vector, calculated from the formula: $\sqrt{x^2 + y^2 + z^2}$; (7) duration of QRS anterior forces; and (8) orientation of the T maximum vector in frontal and transverse planes.

Left ventricular hypertrophy and left and right bundle-branch block were diagnosed according to the conventional electrocardiographic and vectorcardiographic criteria.[24] Abnormal Q and R waves, indicating a "pseudo-infarction" pattern, were diagnosed according to the standard electrocardiographic and vectorcardiographic criteria of myocardial infarction.[24]

STATISTICAL ANALYSIS OF DATA

Standard statistical analyses were performed. Values expressed are means ± 1 standard deviation (SD). The t test was used to test the difference between two means. When the data were not normally distributed, a two-sample Wilcoxon-Mann-Whitney test was used. Comparing the vectorcardiographic data of the relatives under 20 years without asymmetric septal hypertrophy with the normal control subjects, the normal range of the vectorcardiographic measurements refers to the values within two standard deviations of the control group.

Results

(A) ECHOCARDIOGRAPHIC DATA

Asymmetric septal hypertrophy was present in all nine index cases. In these, ventricular septal thickness ranged from 13 to 32 mm.

Four first degree relatives had asymmetric septal hypertrophy: one was a 52 year old man, brother of two affected sisters (family B), one a 20 year old man, son of an affected mother (family C), and two were brothers, 10 and 18 years of age, of a 19 year old affected girl (family D).

Asymmetric septal hypertrophy was absent in 25 relatives. Eighteen of these subjects were under 20 years of age. Ten were male and eight female. Their ages ranged from 4 to 20 years, mean 10·7±6·0.

The corrected thickness of the interventricular septum was abnormal in all the index cases. Three index subjects showed anterior systolic movement of the anterior mitral leaflet and mid-systolic closure of the aortic leaflets.

The corrected thickness of the interventricular septum was abnormal in three of four relatives with asymmetric septal hypertrophy. None of these showed abnormal movement of the mitral or aortic valve.

The echocardiographic measurements in the relatives under 20 years and without asymmetric septal hypertrophy are presented in Table 1 and compared with those of the normal control subjects. The echocardiographic data of the normal controls corresponded to data published for subjects of comparable age.[23] No significant difference was found between

Table 1 *Echocardiographic data in relatives under 20 years of age without asymmetric septal hypertrophy and in normal control subjects*

	Relatives < 20 y (n=18: M 10, F 8)	*Control subjects (n=38: M 18, F 20)*	*P*
Age (y)	10·7±6·0	9·9±5·5	NS
Echocardiographic measurements			
IVS thickness	7·6±1·1	7·4±1·0	NS
IVS thickness corr	5·0±0·8	5·9±0·7	NS
LVPW thickness	7·1±0·9	7·1±0·9	NS
LVPW thickness corr	5·4±0·8	5·6±0·7	NS
LVIDd	42·6±4·1	41·0±4·5	NS
LVIDd corr	33·0±4·5	33·6±5·1	NS
IVS/LVPW ratio	1·0±0·12	1·0±0·10	NS

IVS, interventricular septum; LVPW, left ventricular posterior wall; LVIDd, left ventricular internal dimension at end-diastole; corr, corrected by body surface area.

the relatives under 20 years without asymmetric septal hypertrophy and the control subjects. The interventricular septal corrected thickness was within normal limits in all relatives without asymmetric septal hypertrophy. None of these had abnormal movement of the mitral or aortic valve.

(B) ELECTROCARDIOGRAPHIC AND VECTORCARDIOGRAPHIC DATA

(1) *Index cases*

Four of the nine index cases fulfilled the electrocardiographic and vectorcardiographic criteria of left ventricular hypertrophy with or without strain. Two cases showed abnormal R waves in the right precordial leads and an anteriorly displaced QRS loop in the vectorcardiogram. In one case, abnormal left axis deviation was present. Two subjects had negative T waves in left precordial leads.

(2) *Relatives with asymmetric septal hypertrophy*

Of the four relatives with increased thickness of the interventricular septum, one had a complete right bundle-branch block, one an incomplete left bundle-branch block, and one an abnormal QRS left axis deviation. The electrocardiogram and vectorcardiogram were normal in a fourth.

(3) *Relatives without asymmetric septal hypertrophy*

The vectorcardiographic data in the relatives over 20 years and without asymmetric septal hypertrophy are presented in Table 2. The electrocardiographic and vectorcardiographic measurements were within normal limits in five subjects. Two relatives had an anteriorly displaced QRS loop, that is a Q amplitude in z greater than 0·80 mV.[25] In one of these the R/S ratio in V1 and V2 was >1.[24]

Of 18 relatives under 20 years without disproportionate septal hypertrophy, 13 had normal electrocardiograms. Four young relatives had an R/S ratio in V1 and V2 greater than 1 mm and R V1 amplitude greater than 7 mm.[24] Of these, three were older than 12 years. In one case abnormal left axis deviation of QRS was present. The vectorcardiographic data in the relatives under 20 years without asymmetric septal hypertrophy and in the young normal control subjects are presented in Table 3. The relatives had a significantly greater Q_z voltage ($p<0{\cdot}01$) and Q/R ratio in z ($p<0{\cdot}05$) than the normal control subjects.

Table 2 *Vectorcardiographic data in relatives over 20 years of age without asymmetric septal hypertrophy (seven cases)*

QRS duration (ms)	84·5±11·1
QRS inscription frontal plane	CW 3, CCW 4
QRS inscription transverse plane	CCW 7
QRS MV orientation frontal plane (degree)	+31°±16
Q_z amplitude (mV)	0·55±0·40
R_z amplitude (mV)	1·05±0·30
R_x amplitude (mV)	1·10±0·35
Q/R ratio in z	0·50±0·30
QRS MV voltage TP (mV)	1·40±0·45
QRS MV voltage FP (mV)	1·54±0·54
MLSV voltage (mV)	1·68±0·61
Anterior forces duration in TP (ms)	25±7

CW, clockwise; CCW, counterclockwise; MV, maximum vector; MLSV, maximum leftward spatial vector.

The prevalence of vectorcardiographic abnormalities in the young relatives without asymmetric septal hypertrophy is presented in Table 4. Two standard deviations from the mean of measurements in the control group are considered the normal limit. The vectorcardiographic data in our control group were not significantly different from those already published.[26] All vectorcardiographic measurements were within normal limits in seven of the 18 young relatives (39%). Eleven young relatives without asymmetric septal hypertrophy had some vectorcardiographic abnormalities. Ten of these had Q_z amplitudes greater than 0·80 mV and they were distributed in all the families examined. The subdivision is presented in Table 4. Of these, only two had Q/R ratio in z greater than 1·2. The distribution of Q_z amplitude in young relatives without asymmetric septal hypertrophy and in normal control subjects is presented in Fig. 2. Four young relatives had high voltage of the maximum leftward spatial vector. An abnormal superior orientation of the QRS maximum vector in the frontal plane was observed in three young brothers in family C.

Vectorcardiographic patterns in three relatives under 20 years of age without disproportionate septal hypertrophy are presented in Fig. 3 for purpose of illustration.

Discussion

The electrocardiogram is abnormal in almost every case of hypertrophic cardiomyopathy. Left ventricular hypertrophy, abnormal Q waves, or tall R waves in right precordial leads, ST-T changes, and intraventricular conduction disturbances are the most frequent findings.[12] None of these electrocardiographic abnormalities, however, is pathognomonic of hypertrophic cardiomyopathy.[20] Some investigators described characteristic electrocardiographic or vectorcardiographic patterns in obstructive,[12–16] non-obstructive,[19 21] and apical[27] forms of hypertrophic cardiomyopathy. A definite relation between the electrocardiographic features and the degree of septal hypertrophy or left ventricular outflow tract obstruction,[12] however, has not been established. Consequently, electrocardiograms and vectorcardiograms have been considered secondary aids in the diagnosis of hypertrophic cardiomyopathy.

Table 3 *Comparison of vectorcardiographic features in first-degree relatives under 20 years of age and normal control subjects*

Vectorcardiographic variables	*Relatives*	*Control subjects*	*P*
QRS duration	80·2±9·0	78·2±10	NS
QRS inscription frontal plane	CW 15, CCW 3	CW 37, "8" 1	—
QRS inscription transverse plane	CCW 18	CCW 38	—
QRS MV orientation frontal plane	+40°±21°	+46°±13°	NS
Q_z amplitude	0·80±0·42	0·52±0·17	<0·01
R_z amplitude	1·19±0·34	1·12±0·40	NS
R_x amplitude	1·11±0·42	1·12±0·38	NS
Q/R_z ratio	0·79±0·36	0·53±0·34	<0·05
QRS MV voltage transverse plane	1·52±0·52	1·35±0·45	NS
QRS MV voltage frontal plane	1·54±0·56	1·47±0·57	NS
MLSV voltage	1·71±0·53	1·60±0·48	NS
Anterior forces duration	29·9±6·8	27·5±4·2	NS

CW, CCW, MV, and MLSV as in Table 2; "8", inscription initially clockwise.

Table 4 *Prevalence of vectorcardiographic abnormalities in relatives under 20 years of age without asymmetric septal hypertrophy*

*Vectorcardiographic variable**	*Family A* *2 cases*	*Family B* *7 cases*	*Family C* *8 cases*	*Family D* *1 case*	*Total* *18 cases*
Q_z amplitude >0·8 mV	2	4	3	1	10 (55·6%)
R_z amplitude >1·8 mV	0	0	0	0	0
R_x amplitude >1·8 mV	1	2	2	0	5
Q/R ratio >1·2	0	1	0	1	2
QRS MV angle frontal plane↑+20°	0	0	3	0	3
QRS MV voltage transverse plane >2·3 mV	0	1	0	0	1
MLSV voltage >2·3 mV	0	2	2	0	4
Anterior forces duration > 40 ms	0	1	0	0	1
Total with vectorcardiographic abnormalities	2	4	4	1	11 (61%)
Total without vectorcardiographic abnormalities	0	3	4	0	7 (39%)

*2 SD from the mean of the vectorcardiographic measurements in the young normal control subjects are considered as normal limits.

Nevertheless, previous studies showed a high percentage of electrocardiographic abnormalities in those relatives where asymmetric septal hypertrophy was also found.[1 2] On the other hand, few data have been reported on the electrocardiographic findings in relatives without asymmetric septal hypertrophy. The present study shows that a relatively large number of relatives of subjects with documented hypertrophic cardiomyopathy may have vectorcardiographic abnormalities, even though the echocardiogram is normal.

The most interesting observation is that ten out of 18 relatives under 20 years of age without asymmetric septal hypertrophy had increased voltage of the anterior forces on the orthogonal electrocardiogram (Q_z greater than 0·80 mV). Moreover, in each of the four families, at least one young relative who was considered to be unaffected on the basis of echocardiographic findings, had high amplitude of the anterior forces. Other abnormal and less commonly observed vectorcardiographic features included increased voltage of leftward QRS forces (R_x greater than 1·8 mV)

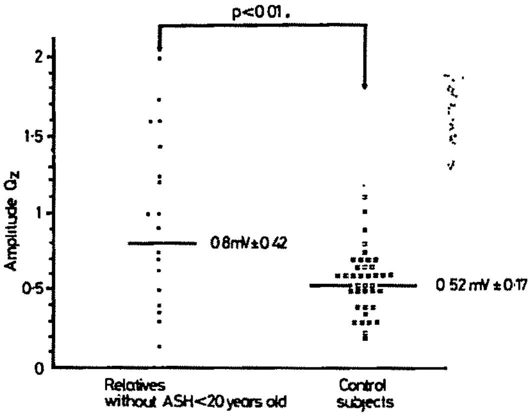

Fig. 2 *The diagram shows the amplitude of the anterior forces of the QRS in the orthogonal electrocardiogram (Q_z voltage) in the relatives under 20 years of age without asymmetric septal hypertrophy (ASH) and in 38 normal control subjects of comparable age range.*

and pronounced superior orientation of QRS maximum vector in the frontal plane.

The standard electrocardiogram was within normal limits in 13 young relatives without disproportionate septal hypertrophy; this reflects a higher sensitivity of the vectorcardiogram in detecting increased QRS anterior forces. In fact, 11 young unaffected relatives showed vectorcardiographic abnormalities, but only one of them had increased voltage of QRS anterior forces.

The discrepancy between the electrovectorcardiographic and echocardiographic findings in so many relatives without asymmetric septal hypertrophy is difficult to explain.

First of all, the reliability of the diagnosis of asymmetric septal hypertrophy on the basis of the septal to free wall ratio[3,28] is still controversial. It is well known that even minor errors in the measurement of the septal and posterior wall thickness may strongly influence the septal/posterior wall ratio, thereby hindering a correct classification of subjects with borderline ratios.[2] In our study, however, none of the relatives classified as unaffected had clinical evidence of hypertrophic cardiomyopathy[11] or had other abnormalities at M-mode echocardiography.[28] Furthermore, concentric hypertrophy of the left ventricle, sometimes found in hypertrophic cardiomyopathy,[27,29,30] was absent in all cases.

On the other hand, an anterior displacement of the QRS loop may result from a variety of conditions such as right ventricular enlargement, ventricular preexcitation, right ventricular conduction defect, or true posterior myocardial infarction.[21] Such a pattern has also been noted as a relatively common normal variant.[19] All these causes, however, were excluded in our subjects on the basis of the clinical, electrocardiographic, and echocardiographic findings. In addition, the young relatives without asymmetric septal hypertrophy had increased amplitude of the anterior forces ($p<0{\cdot}01$) and greater anterior/posterior forces ratio ($p<0{\cdot}05$) compared with normal controls, though the echocardiographic data were not significantly different. Thus, in this study the vectorcardiographic features observed in the young relatives without asymmetric septal hypertrophy should be considered as true abnormalities.

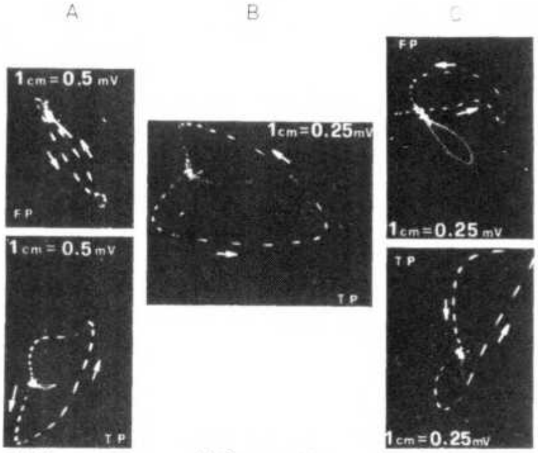

Fig. 3 *Examples of vectorcardiographic patterns in relatives under 20 years of age without asymmetric septal hypertrophy. (A) and (B) increased voltage of the QRS anterior forces in the horizontal plane. (C) Abnormal superior orientation of the maximum vector of the QRS in the frontal plane.*

M-mode echocardiography is commonly considered a sensitive means for the identification of hypertrophic cardiomyopathy.[28] One must be cautious, however, in diagnosing or excluding the disease by M-mode echocardiography alone.[31] DeMaria *et al.*[32] emphasised that wide angle two dimensional echocardiography may decrease the false positive diagnoses of asymmetric septal hypertrophy and may recognise unusual locations of left ventricular hypertrophy, such as the predominant concentric hypertrophy in the apex reported by Yamaguchi *et al.*[27] Maron *et al.*[29] recently reported other unusual locations of hypertrophic cardiomyopathy undetectable by M-mode echocardiography. In these cases the electrocardiogram was abnormal and represented a more sensitive marker than M-mode echocardiography.[29] Consequently, hypertrophic cardiomyopathy should not be ruled out on the basis of M-mode echocardiography alone when other clinical data suggest the diagnosis.[29]

For ethical reasons we did not perform invasive investigations on the relatives who did not show echocardiographic abnormalities. Unfortunately, two dimensional echocardiography was not obtained. Hence, in the absence of solid confirmatory data, we can only suggest alternative hypotheses to explain the significance of the vectorcardiographic abnormalities observed in the relatives without evidence of asymmetric septal hypertrophy.

First, these subjects could represent M-mode echocardiographic false negatives of atypically distributed hypertrophic cardiomyopathy: hypertrophy of the posterior interventricular septum, the anterolateral free wall, or the apical portion of the septum, which were not detected by M-mode echocardiography, were present in 18% of the subjects reported by Maron *et al.*[30]

Second, the vectorcardiographic abnormalities could indicate an "occult" cardiomyopathy and precede the development of cardiac hypertrophy. This hypothesis is consistent with the data of Maron *et al.*,[30] who reported electrocardiographic abnormalities in five young subjects with documented family history of hypertrophic cardiomyopathy and without any M-mode or two dimensional echocardiographic evidence of actual disease.[29]

Finally, increased voltage of QRS anterior forces may represent a marker not related to actual cardiac involvement in some familial forms of hypertrophic cardiomyopathy, as in relatives of subjects with Duchenne's progressive muscular dystrophy.[33 34]

On the other hand, the electrophysiological mechanism determining tall R waves in the right precordial leads in many subjects with documented hypertrophic cardiomyopathy is still debated: either a disproportionate hypertrophy of the interventricular septum or a conduction disturbance of septal and apical areas could displace the QRS loop anteriorly and to the left.[35 36] Conclusive evidence of a relation between this electrocardiographic feature and anatomical features of cardiomyopathy[19] is, however, lacking.

Similarly, the clinical significance of abnormal anterior forces in the young relatives without asymmetric septal hypertrophy will probably be clarified only after follow-up. Moreover, definite conclusions cannot be drawn from the relatively small number of families examined.

In conclusion, we suggest that the observation of increased anterior QRS forces in one or more first degree relatives of a subject with documented hypertrophic cardiomyopathy may be a valuable aid in ascertaining the genetic transmission of the disease, complementing the echocardiographic data.[37] The same feature might also be used to recognise affected or potentially affected members without echocardiographic evidence of asymmetric septal hypertrophy.[29]

We thank Mr Mario Iannarelli for technical and statistical assistance.

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Non-invasive diagnosis and assessment of tricuspid regurgitation and stenosis using one and two dimensional echo-pulsed Doppler

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SUMMARY Twenty normal subjects and 82 patients with valvular heart disease, whose lesions were independently assessed either by cardiac catheterisation and/or at operation, were studied using the pulsed Doppler technique combined with either one or two dimensional echocardiography. Of these, 41 patients had tricuspid lesions, including 40 with regurgitation and nine with stenosis. The tricuspid analogue flow velocity trace and the Doppler frequency spectrum (time interval histogram) were recorded. Characteristic differences were found between the records from subjects with and without tricuspid lesions. In subjects with tricuspid regurgitation there was a systolic negative wave on the analogue velocity display and broadening of the time interval histogram. In subjects with tricuspid stenosis there was an abnormal pattern, and significantly increased duration of the diastolic wave on the analogue velocity trace, again with broadening of the time interval histogram. Sensitivity and specificity ranged between 85 and 95%. The calculated ratio between the measured amplitudes of the systolic and diastolic waves correlated well with independently performed grading of the regurgitation on a three point scale in 85% of cases. Grading of the severity of tricuspid stenosis on a three point scale based on studies of the diastolic Doppler velocity anomalies was the same in 85% of cases as the grading based on established invasive techniques. The addition of two dimensional echocardiography to the pulsed Doppler technique increased the sensitivity for mild lesions.

Invasive procedures do not solve all the diagnostic problems raised by tricuspid lesions,[1-5] in spite of some helpful contributions from dye dilution,[2] intracardiac phonocardiography,[6 7] and angiography.[8] Echocardiography,[9-11] even when combined with contrast injections for the study of tricuspid regurgitation,[12 13] often lacks sensitivity and may give nonspecific diagnostic information, since it relies on peripheral or indirect data, such as motion of the interventricular septum. As early as 1970, continuous wave Doppler provided information on systemic venous return and led to a new diagnostic method for the evaluation of tricuspid disease.[14-16] The crucial advantage of pulsed Doppler, combined with either one dimensional[17-24] or two dimensional[25] echocardiography, is that it provides direct data from the site of the lesions. The present study was undertaken to evaluate the reliability of this new method when applied both to regurgitation and stenosis.

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Subjects and methods

The study population included 20 normal subjects (12 women and eight men, mean age 28 years), and 82 patients (50 women and 32 men, mean age 38 years) in whom the presence of a tricuspid lesion was confirmed or ruled out using classical invasive procedures, that is right heart catheterisation (77 cases), with right ventricular angiography in 20 cases, intracardiac phonocardiography in seven cases, dye dilution curves in nine cases, and assessment of the tricuspid valve at the time of surgery in 38 cases. Diagnoses included mitral lesions, pure (45) or combined with aortic valve (22) and/or tricuspid valve (21) disease, isolated aortic valve lesions (14), acute tricuspid endocarditis (four), chronic endomyocardial fibrosis (five), mitral and tricuspid prolapse (four), and congenital heart disease (10). Forty-seven patients were in sinus rhythm and 35 in atrial fibrillation.

DIAGNOSIS OF TRICUSPID LESIONS

Tricuspid lesions were present in 41 patients consisting of 40 cases of regurgitation, eight of whom had associated stenosis, and one case of pure stenosis. With one exception the diagnosis was substantiated by at least two invasive procedures.

CLASSIFICATION OF TRICUSPID LESIONS

The severity of the tricuspid lesions was graded independently from the ultrasound findings on a three point scale, using the maximum information available in each case from cardiac catheterisation, pressure measurements, dye dilution, right ventricular angiography, and the surgical findings. This independent grading was grade 1 mild (19 lesions), grade 2 moderate (22 lesions), and grade 3 severe (eight lesions).

APPARATUS

We used an ATL* 3 MHz pulsed Doppler velocimeter, combined either with a one dimensional echocardiograph (ATL 500 A), or with a two dimensional 90° wide angle mechanical sector scanner (ATL 851). Each device uses a single transducer for both techniques. The diameter of the transducer is 1·2 cm for the ATL 500 A, and 2·5 for the ATL 851. According to the Doppler principle, the range gating system makes it possible to record the velocity of a small blood sample (2×4 mm) at any given location along the ultrasonic beam from 3 to 17 cm.[26] The output consists of three signals: (1) an audiosignal of the Doppler shift, (2) the time interval histogram, a form of spectral display of the Doppler signal, and (3) the analogue flow velocity trace. These two displays have been well described;[26] in brief, the time interval histogram is produced by measuring the interval between two successive zero crossings of the Doppler audiosignal; the instantaneous Doppler shift is defined as the reciprocal of this interval; a dot is printed on the strip chart paper at a distance from the zero line which is directly proportional to the Doppler shift frequency. The analogue flow velocity trace corresponds to the mean value of the Doppler frequency shift and is obtained by frequency-to-voltage conversion of the audiosignal using zero crossing detection technique; its polarity may be reversed by a switch on the recorder.

We also used two video monitors, one for the real time scanning, and the other for the Doppler display. Recordings were made on a Sony video tape recorder. Hard copies of real time imaging were obtained on a 4633 Tektronix recorder. Doppler analogue flow velocity traces, TM echocardiographic tracings, Doppler spectral displays, as well as simultaneous electrocardiograms lead II, and frequency selecting phonocardiograms were recorded on an Irex I† fibreoptics recording system.

RECORDING METHOD

Tricuspid Doppler recordings were obtained by locating the transducer at the lower parasternal edge when using the one dimensional echo Doppler (37 cases).[17] For two dimensional echo Doppler, we used the parasternal short axis (aortic valve and left ventricular level), apical four chambers, and subcostal views (45 cases), previously described for normal hearts.[25]

In brief, two dimensional echo Doppler recordings always required successively: (1) dynamic scanner visualisation of the tricuspid valve, (2) location of the Doppler beam at the desired angle to the tricuspid valve, (3) adjustment of the Doppler gate to control the depth of the sample volume along that beam. This was achieved by obtaining a good two dimensional scan of the right heart cavities and of the tricuspid valve, and then the axis of the Doppler beam seen as a continous white line was swept across the scan plane by moving a lever on the probe until it crossed the tricuspid valve at the desired angle. The Doppler gate, seen as a bright spot, was adjusted using a control on the probe. The image was then frozen while the apparatus was automatically switched to the Doppler system. When the characteristic Doppler sound was heard, the recording was made. We recorded several samples at the annulus: at least one at the centre of the annulus and one at the commissures.

VARIABLES STUDIED

The study involved the analysis of both the analogue and the spectral displays.

(1) Analogue flow velocity traces

These were examined for the presence or the absence of a systolic negative wave, its amplitude, duration, and spatial annular extension, and also for the diastolic pattern.

(a) When a negative wave was present, an index of its magnitude was calculated: the negative/positive (N/P) ratio. This was obtained for each recording in the following manner (Fig. 1): the amplitude of the negative wave was measured at two points in systole, the first (N1) 70 ms after the first heart sound, and the other (N2) 70 ms before the second heart sound as shown on the phonocardiogram. The maximum diastolic positive deflection (P) from the trace was measured and the mean of the ratios N1/P and N2/P was calculated; that is $\frac{N1/P+N2/P}{2}$. This value was obtained for each recording. Where there were only two recordings, the mean of the two N/P values was

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† Irex, Mahwah, NJ, USA.

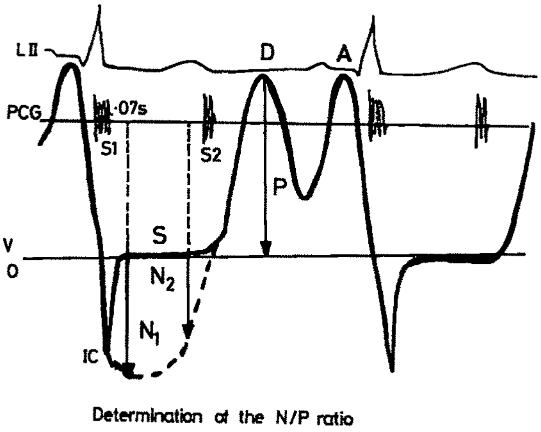

Fig. 1 *Schematic representation of the tricuspid flow velocity trace, with determination of the N/P ratio (systolic segment: full line, normal; thick dashed line, abnormal negative wave seen in patients with tricuspid regurgitation; V, analogue flow velocity trace; 0, zero line; LII, lead II of the electrocardiogram; PCG, phonocardiogram; S1 and S2, first and second heart sounds; IC, brief negative deflection caused by the isometric contraction; S, systolic segment; "D" and "A", early- and end-diastolic positive filling waves; N1 and N2, amplitude of the negative wave calculated in centimetres from the zero line; P, maximal amplitude of the positive diastolic wave calculated in centimetres from the zero line). The systolic negative depth is measured in two points of systole: −0·07 s after the end of the first heart sound (N1), and −0·07 s before the second sound (N2); it is then related to the amplitude of the "D" wave (P); the same manoeuvre is repeated on another blood velocity sample examined at the annulus, and the overall mean is calculated.*

calculated. Where more than two recordings were available, the most disparate values of N/P were used to obtain the mean. Where one of these was zero, the other value was divided by two.

(b) The duration of the early diastolic filling wave (D) was measured for patients with atrial fibrillation. The time interval was corrected for heart rate by the Bazett[27] formula. The mean of values from five cardiac cycles was obtained for each recording.

(2) Frequency spectrum

This was examined for the presence or absence of a spectral broadening when the Doppler sample volume was at any point of the annulus or in the right atrium. Spectral broadening was considered abnormal when the dispersion of the dots was present on the time interval histogram according to the following criteria: (1) use of the minimal Doppler gain compatible with the recommended signal to noise ratio judged from the bottom trace on the monitor called "signal amplitude" (Fig. 2), (2) amplitude of the dispersion at least twice as wide as that seen on the spectrum for laminar flow in segments of the same cardiac cycle, (3) duration of the disturbance equal to or greater than 0·10 s, and (4) absence or interference from any cardiac structure motion.

Analysis of the Doppler data was made without knowledge of the results of the invasive procedures. A statistical analysis of the results was performed using a Hewlett Packard 4815 with determination of: (1) the mean value and standard deviation for the duration of the diastolic filling (D) wave in cases of atrial fibrillation and for the N/P radio in cases of regurgitation; (2) the significance of the differences found between different grades of severity for the latter, assessed using the Student test (t and P); (3) the linear regression equations between the calculated Doppler data and the haemodynamic variables.

Results

NORMAL SUBJECTS

Fig. 2 shows the normal pattern of the tricuspid flow velocity trace both for analogue and spectral display, using the two dimensional echo Doppler. Neither an abnormal spectral broadening nor a systolic negativity was noted during the cardiac cycle.

PATIENTS WITH TRICUSPID LESIONS

Diagnosis

(1) *Tricuspid regurgitation* (Figs. 3 and 4). The presence of an abnormal systolic negative wave and/or of a spectral broadening was noted in 41 patients. In 35 of these patients, tricuspid regurgitation was proven (sensitivity: 87%, and specificity: 85%). Five false negative diagnoses were found in patients with mild regurgitation, four of whom were studied with one dimensional echo Doppler only. False positive diagnoses were equally common using the two echo procedures.

(2) *Tricuspid stenosis* (Fig. 5). In 10 cases, diastolic abnormalities were found on the velocity recordings where the corresponding Doppler sound was higher pitched; with the Doppler sample at one or several points of the annulus, the "D" summit of the analogue trace was cut off and replaced by an indented horizontal plateau or gently ascending slope with broadening of the corresponding part of the spectrum. In six patients with atrial fibrillation, a significant increase in duration of the "D" wave was noted (Table 1 and Fig. 6). Of these 10 cases, tricuspid stenosis was confirmed in eight cases by the invasive data: the ninth case of proven stenosis was not found by Doppler (sensitivity: 88%, specificity: 97%). In one false positive case, external compression of the tricuspid annulus caused by a huge left atrium was found during operation. Fig. 7 illustrates the overall results (sensitivity, specificity, predictive value, and accuracy of the method).

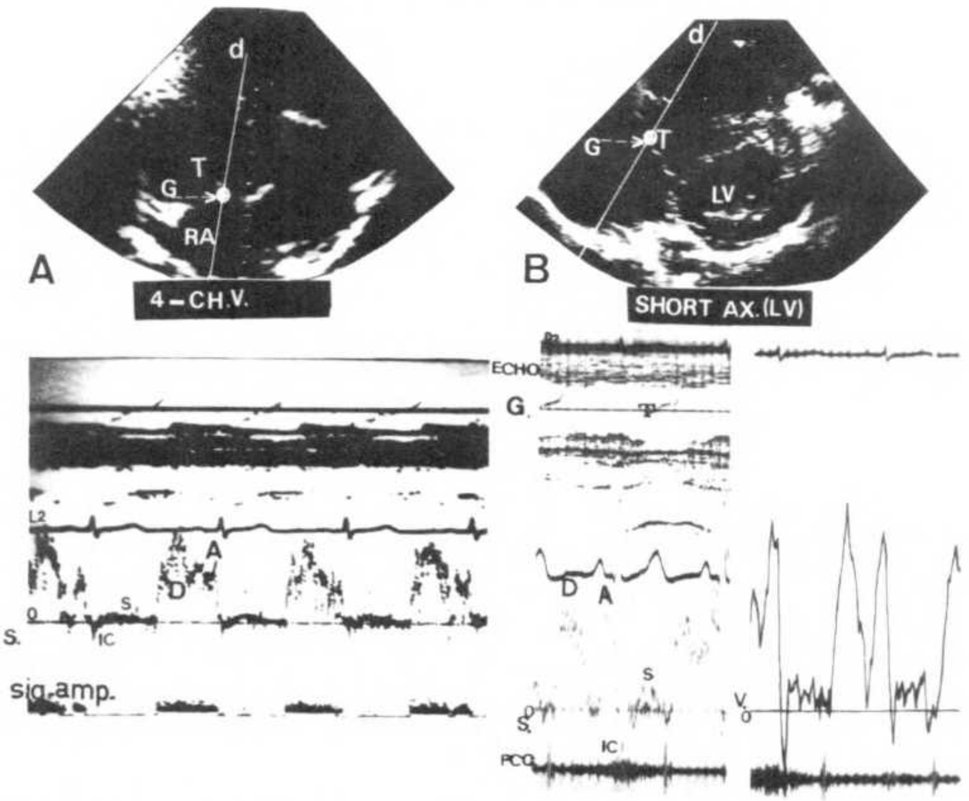

Fig. 2 *Normal subject: tricuspid flow velocity trace obtained using two dimensional echo Doppler (d, Doppler beam; T, tricuspid valve; G, Doppler gate; RA, right atrium; LV, left ventricle; ECHO, TM echocardiographic visualisation; S, frequency spectrum (time interval histogram); sig. amp., signal amplitude; other abbreviations as in Fig. 1). Here, two different approaches are used to visualise the tricuspid valve: (A) on the left, using the apical four chamber view, (B) on the right, using the left ventricular short axis view; the Doppler gate (seen as a white point) has been moved along the Doppler beam (seen as a white line) to the level of the tricuspid valve: the characteristic normal tricuspid flow velocity pattern is displayed, both on the spectrum (bottom left and middle) and on the analogue (bottom right). Four segments are shown: the "ic" deflection lined up with the first sound; the "S" segment near to the zero line because of the absence of forward flow in systole and the two positive waves of forward flow, the early diastolic "D", and the end-diastolic "A" related to atrial contribution to the ventricular filling. Note the smooth pattern of the diastolic summits, and the absence of any noticeable spectral broadening. In A, the gate was intentionally located a little higher than the annulus to show the effects of the valvular motion on the spectrum: brief transient dispersion of the dots is elicited, without pathological significance.*

Assessment of severity of lesions

(1) *Tricuspid regurgitation* (Fig. 8 and Table 2). A significant increase in the N/P ratio between each grade of severity was found. Satisfactory grading of severity was obtained from Doppler data in 85% of cases, with two underestimations and one overestimation.

(2) *Tricuspid stenosis*. The assessment of the severity was satisfactorily obtained in 87% of cases, with one overestimation. The indented pattern was found at the commissures in two mild lesions out of three, and spread nearer to the centre in the five cases of moderate stenoses. No satisfactory recording could be obtained in diastole in one case of severe stenosis.

Correlations between N/P ratio, diastolic filling wave duration, and haemodynamic variables (Tables 1 and 2) No significant difference between the three grades of severity was found for the mean value of the "v" wave, the mean right atrial pressure, or the systolic right ventricular pressure. No satisfactory linear correlation was found between those variables and the measurements performed on Doppler data.

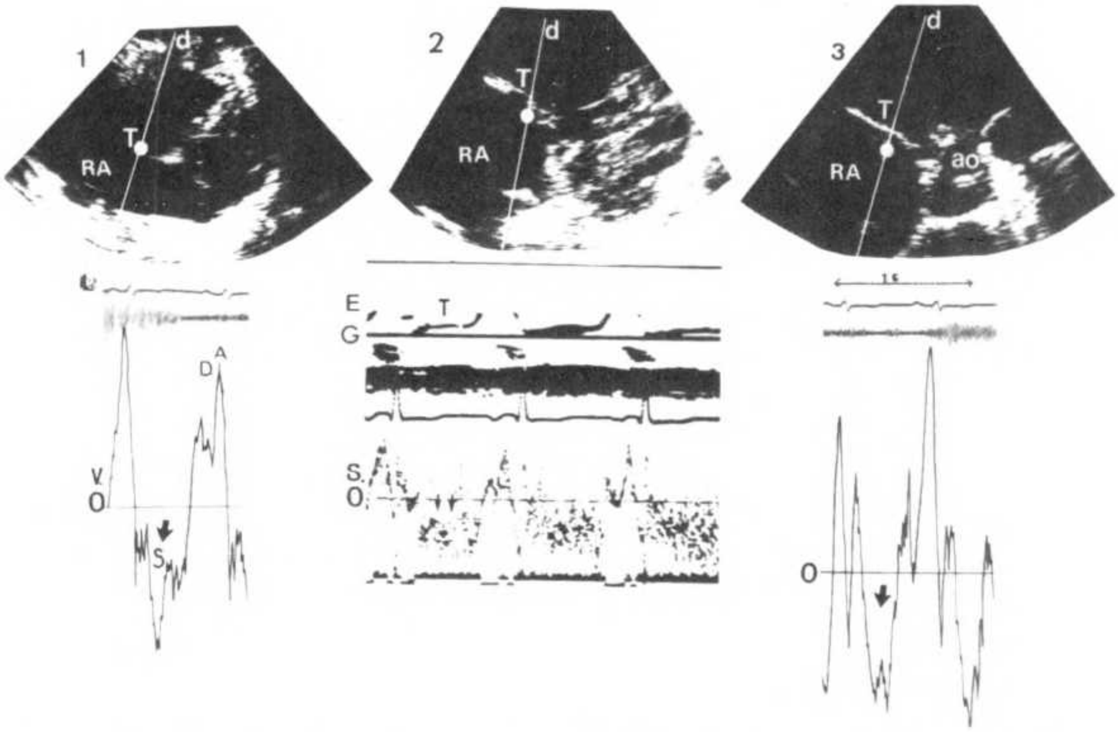

Fig. 3 *Chronic endomyocardial fibrosis with severe tricuspid regurgitation (same abbreviations as in Fig. 2, ao, aortic valvular area). (1) Four chamber view: the gate is located at the level of the tricuspid valve and the bottom panel shows a conspicuous negative S wave (thick arrow). (2) Left ventricular short axis view: the spectral curve at the bottom is abnormal in systole, showing pronounced and prolonged broadening with presence of backward flow (small arrows). (3) Aortic valvular area short axis view: the abnormal systolic negative wave is also displayed using this approach. No normal systolic pattern could be recorded in this case of severe regurgitation resulting from annular dilatation.*

PATIENTS WITHOUT TRICUSPID LESIONS

With the exception of the false Doppler diagnoses already mentioned the recordings were similar to those of normals. Disappearance of the "A" wave was observed in cases of atrial fibrillation; the "D" wave was normal in these patients (Fig. 9).

Discussion

The comments will be focused on (1) the technical limitations of the pulsed Doppler technique, (2) the recall of the respective advantages of one and two dimensional echo Doppler, (3) the results for regurgitation, and (4) stenosis.

(1) TECHNICAL LIMITATIONS

Though the empirical relations between the velocity traces obtained and the flow disturbances of tricuspid valve disease cannot be disputed, and the shapes of the velocity traces both in normal subjects and in those with tricuspid valve disease are similar to those recorded using continuous wave Doppler catheters[15] and electromagnetic flowmeters,[28] there are technical limitations of the technique which put some constraints on the interpretation of these velocity traces. (1) Absolute velocities cannot be calculated since the angle θ between the ultrasound beam and blood flow direction is unknown, and neither the time interval histogram nor the analogue velocity display are calibrated. (2) Pulsed Doppler imposes a conflict between the use of high pulse repetition frequency for the measurement of high velocities and the lower pulse repetition frequency required for recordings at any depth, the so-called "Nyquist limit". (3) Spectral broadening on the time interval histogram, commonly accepted as an indication of turbulence in the sample volume, may also arise if the Nyquist limit is exceeded and is very susceptible to observer control.

Some of these limitations are less serious for tricuspid valve disease than for mitral valve disease, since the tricuspid valve is closer to the chest wall and the blood velocities tend to be lower.

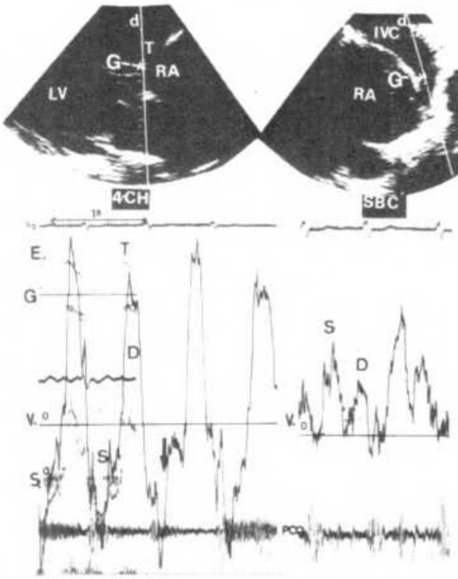

Fig. 4

Fig. 4 *Moderate tricuspid regurgitation: tricuspid versus caval detection for the diagnosis of the regurgitation (same abbreviations as in previous figures, SBC, subcostal approach; IVC, inferior vena cava). On the left, four chamber view, the gate is located at the tricuspid valve: signs of tricuspid regurgitation are elicited on the Doppler displays at the bottom (thick arrow lining with the systolic negative wave). On the right, the gate is moved towards the vena cava, using the subcostal approach: the regurgitation is missed since there is a normal pattern of the systolic part of the caval flow velocity.*

Fig. 5 *Pulsed Doppler recordings in tricuspid stenosis (same abbreviations as before, M, mitral valve; TIH, time interval histogram). This figure shows two recordings at the tricuspid valve: in 1 (top left panel), the gate has been located at the centre of the tricuspid orifice (indicated by 1 on the scanner view in the middle panel): though some indentations may be seen on the analogue trace, the general normal diastolic pattern is recognisable with the separate "D" and "A" waves. In 2 (top right panel) the gate has been located next to the commissural area (indicated by 2 on the scanner view): a typical stenosed indented pattern is recorded with progressive ascent toward the end of the diastole (oblique arrows). This patient had a mild pure stenosis with a pressure gradient of 3 mmHg. This figure shows the need for several Doppler recordings at a given orifice, in order not to miss a mild lesion.*

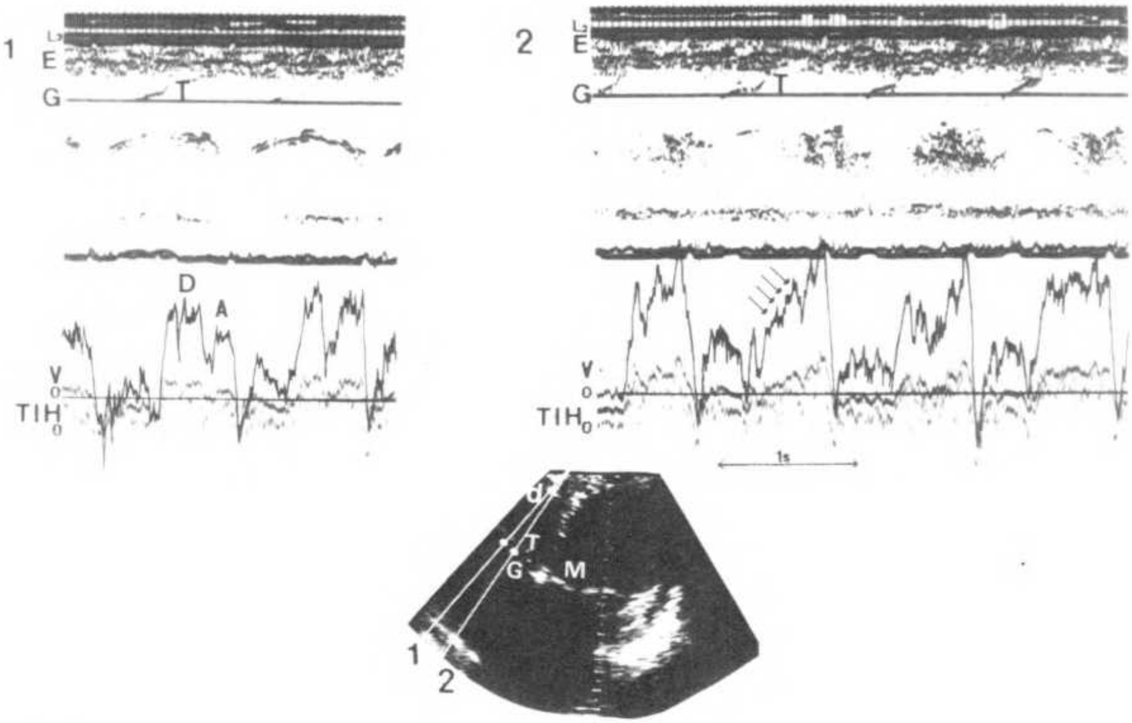

Fig. 5

Table 1 *Duration of filling "D" wave in patients with atrial fibrillation with and without tricuspid disease*

	Patients without tricuspid disease	*Patients with tricuspid regurgitation*	*Patients with tricuspid stenosis*
No. of subjects	12	12	6
Duration of filling "D" wave (c)*	0·29±0·04	0·33±0·06**	0·51±0·06***

Correlation between mean right atrial pressure/DFW: $y=17{\cdot}92.x+1{\cdot}46$ $r=0{\cdot}41$.

*Duration of filling "D" wave (c), with correction for heart rate, expressed in seconds.

***$p<0{\cdot}001$; **$p<0{\cdot}05$.

Note: Significant increase in duration of forward flow in cases of organic stenosis obvious in spite of the limited number of stenotic cases and of the discrete character of the stenosis in a third of the cases. No satisfactory linear correlation appears between this duration and the value of the mean of the right atrial pressure.

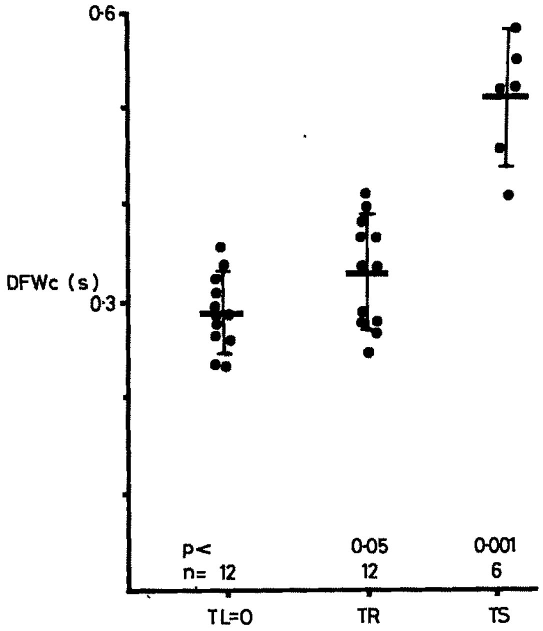

Fig. 6 *Duration of the filling wave in patients with and without tricuspid lesion and with atrial fibrillation (TL=0, patients without tricuspid lesions; TR, tricuspid regurgitation; TS, tricuspid stenosis; DFWc, duration of the diastolic filling wave "D", with correction for heart rate). The mean values (horizontal bars) and the standard deviations (vertical bars) are indicated, and also the individual values. A significant increase of the duration of the "D" wave was observed in patients with stenoses.*

One of our criteria for the assessment of a disturbed spectrum needs some comment: the reference to a normal segment in the cardiac cycle could be inadequate when combined lesions are present, but, in our experience, it was always possible to find a normal segment for comparison in such cases.

(2) TWO DIMENSIONAL ECHO DOPPLER VERSUS ONE DIMENSIONAL ECHO DOPPLER

The placement of the sample volume was much easier with the two dimensional echo which enabled a more accurate investigation of the annulus and of the commissures. This fact probably explains the lower rate of false negative results for the diagnosis of mild regurgitation when using this apparatus. On the other hand, the signal to noise ratio was less good for the Doppler, and the probe less handy in this equipment than in the one dimensional device.

(3) RESULTS FOR TRICUSPID REGURGITATION

Fig. 4 illustrates the need for recording direct data on tricuspid flow disturbances for a reliable assessment of lesions. This requirement is fulfilled by the use of the pulsed Doppler technique. We have already mentioned the advantages of the use of the two dimensional equipment for avoiding false negative results.

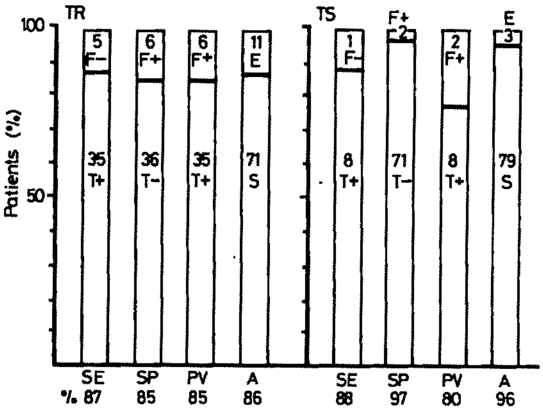

Fig. 7 *Correlative data between pulsed Doppler echocardiography and invasive procedures for diagnosis of tricuspid lesions (TR, tricuspid regurgitations; TS, tricuspid stenosis; SE, sensitivity; SP, specificity; PV, predictive value; A, accuracy of the method; F+, false positive diagnoses using pulsed Doppler; F−, false negative diagnoses using pulsed Doppler; T+, true positive diagnoses using pulsed Doppler confirmed by invasive procedures; T−, true negative diagnoses using pulsed Doppler confirmed by invasive procedures; S, total successful diagnoses using pulsed Doppler; E, total wrong diagnoses using pulsed Doppler).*

Table 2 *Value of N/P ratio and of haemodynamic variables involved in correlative study for patients with tricuspid regurgitation*

	Tricuspid regurgitation				
No. of patients	*Grade 1*	*Grade 2*	*Grade 3*		
(34)	*(9)*	*(19)*	*(6)*		
N/P	*0·21±0·11*	*0·44±0·15* *	*0·75±0·11* **	*Correlation between N/P ratio and haemodynamic variables (n=28)*	
"v" wave	6±3	11±4	14±8	v wave=6·49 N/P+7·34	r=0·26
Mean right atrial pressure (mmHg)	7±3	9±3	10±4	Mean right atrial pressure (mmHg)=2·79 N/P+7·54	0·14
Right ventricular systolic pressure (mmHg)	39±13	45±16	45±31	Right ventricular systolic pressure= −4·49 N/P+43·82	0·02

N/P, ratio of amplitude of negative systolic wave, related to that of the diastolic positive wave.
*p<0·01.
**p<0·001.

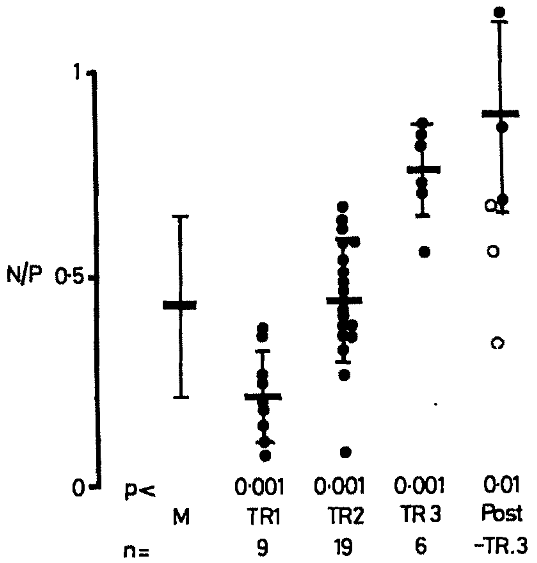

Fig. 8 *Semiquantitative assessment of severity of regurgitation using N/P ratio. Left column, overall mean (M) (horizontal bar) with the standard deviation (vertical bar) for the patients with tricuspid regurgitation (TR); second to fourth columns: mean values of the N/P ratio according to the grading of increasing severity (1 mild, 2 moderate, 3 severe); p, p values for each grade of severity; last column on the right: three patients were examined before (○) and after (●) removal of the tricuspid valve (Post-TR); the tricuspid removal was followed by a significant increase in the N/P ratio.*

In spite of these advantages and resultant more accurate checking of the sample, the false positive percentage was equal for both types of equipment. Since there is no gold standard for evaluation of tricuspid regurgitation, one logical explanation for our findings of negative systolic velocity at the tricuspid annulus in some patients not diagnosed as having tricuspid regurgitation was that the Doppler technique is more sensitive and, therefore, superior to other techniques of tricuspid valve assessment. Among these, angiography appeared the most reliable, as we found only one false positive Doppler diagnosis when this procedure was used for the correlative study.

The correlation of both displays (analogue and spectral) increased the diagnostic sensitivity; the reason was that some cases of mild regurgitation could only be shown on the spectrum and not on the analogue display, and, conversely, some cases of free regurgitation, described as "silent" during intracardiac phonocardiographic procedures,[6] coexisted with apparently laminar flow. Two different procedures have been described to assess the severity of the tricuspid regurgitation: an index of systolic turbulence[23] and the calculation of the N/P ratio[22]; in our experience, the characteristics in amplitude and duration of the spectral broadening appeared less reliable than the calculation of the N/P ratio, and were not taken into account for grading the severity. The evaluation of the severity therefore only relied, in the present study, on the measurement of the N/P ratio; we are aware that at least three factors prevent an accurate quantification of tricuspid regurgitation: (1) the somehow arbitrary selection of the two samples at the annulus, (2) the unknown angle θ which, moreover, could vary if the heart moves and if forward and reverse flow are not at 180° to each other, and (3) the variations in size of the tricuspid annulus during the cardiac cycle.[29] In spite of these limitations, our index proved to be clinically very useful for a semiquantitative evaluation of tricuspid regurgitation. Discrepancies in Doppler grading were generally related to unrepresentative samplings in the presence of low cardiac output leading to underestimation, or of exceptionally poor echo visualisation. The lack of satisfactory correlation between the N/P ratio and the haemodynamic variables may be explained by the presence of nearly normal pressures in several patients with significant lesions.

(4) RESULTS FOR TRICUSPID STENOSIS

These preliminary results suggest high diagnostic reliability of the pulsed Doppler technique. In two cases, the Doppler technique appeared even more

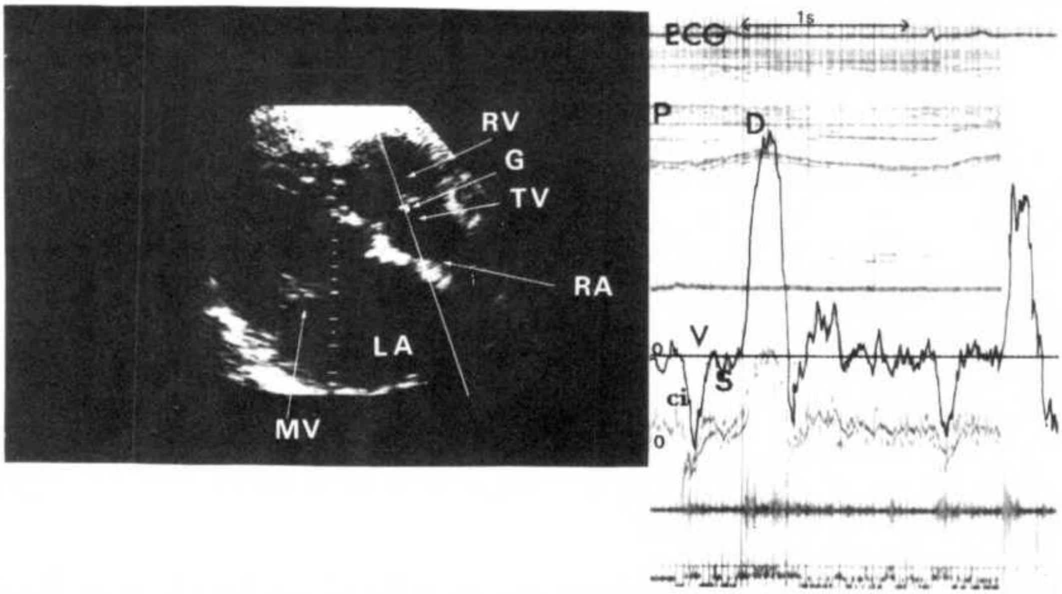

Fig. 9 *Tricuspid flow velocity recording in patient with atrial fibrillation but without tricuspid lesion (same abbreviations as in previous figures, MV, mitral valve; LA, left atrium; RV, right ventricle; TV, tricuspid valve). There is a disappearance of the "A" wave with an early diastolic "D" wave of normal duration. The systolic wave is normal. (Each vertical bar interval=0·04 s.)*

reliable than cardiac catheterisation since Doppler studies showed anomalies, diagnostic of tricuspid stenosis, where cardiac catheterisation disclosed no significant tricuspid pressure gradient; at operation, the valve was found to show commissural fusion and appeared typically stenosed. Severe tachyarrhythmia was the reason for a false negative result in one case where no adequate diastolic flow recording could be obtained. External compression of the orifice was found to have the same consequences upon flow as valvular stenosis and may, therefore, occasionally cause confusion.

The significantly increased duration of the early diastolic filling wave was a reliable and sensitive sign of stenosis in patients with atrial fibrillation, where the lack of "A" wave could make the pattern anomalies less obvious. This timing anomaly helped to avoid confusion with the increased diastolic flow component seen in patients with severe regurgitation, since there is no appreciable overlap between the respective values in both groups (Fig. 6). The evaluation of the severity was not based on the time interval histogram because of its limitations; a more quantitative approach may be expected from the use of Doppler real time spectral frequency analysers recently available. For instance, the analysers may perform the transform by numerous multiplications and additions of discrete Doppler time samples with frequency sweeps called "chirps" (Z chirp transform),[30] or may use a digital fast Fourier transform.[31] In our study, the assessment relied on a pattern recognition method taking into account the central and commissural velocity patterns which appeared clinically reliable. No relation between the duration of the filling wave and the severity of the stenosis could be established in our limited number of cases, and this needs further investigation.

Conclusion

Provided that some methodological rules are observed, the pulsed Doppler technique seems the most reliable non-invasive method so far developed for assessment of tricuspid lesions; its reliability was maintained even in patients with atrial fibrillation and heart failure, and was independent of the level of right ventricular pressure.

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Atrial fibrillation—a marker for abnormal left ventricular function in coronary heart disease

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SUMMARY Retrospective study of 1176 patients with known coronary heart disease by cardiac catheterisation disclosed 10 patients (0·8%) with atrial fibrillation. Comparison with 25 randomly selected patients with coronary heart disease with sinus rhythm showed that atrial fibrillation correlated significantly with impaired haemodynamic function, mitral regurgitation, and abnormalities of left ventricular contraction. Atrial fibrillation is, therefore, a useful marker of extensive myocardial dysfunction.

Although the prognosis of atrial fibrillation in acute myocardial infarction has received widespread attention,[1-3] the significance of this arrhythmia in chronic coronary heart disease has not been evaluated. In this study, we reviewed 1176 consecutive patients undergoing cardiac catheterisation and angiography for coronary heart disease. The clinical and haemodynamic data of 10 patients with chronic atrial fibrillation were compared with a randomly selected control population of 25 patients with coronary heart disease in sinus rhythm in order to examine the association of this arrhythmia with clinical course and haemodynamic function.

Subjects and methods

In the three year period between 1973 and 1976, 1176 patients who underwent cardiac catheterisation were found to have coronary heart disease. These patients were catheterised for known or suspected coronary heart disease or for the evaluation of chest pain. In addition to a complete history and examination, all had a 12 lead electrocardiogram, posterior-anterior and lateral chest *x*-rays, and right and left heart catheterisation, including left ventricular angiography and coronary arteriography. Patients with primary valvular heart disease, such as congenital or rheumatic valvular disease, and primary myocardial disease were excluded. The diagnosis of atrial fibrillation was made on the basis of accepted criteria.[4] Chronic atrial fibrillation was defined as persistent atrial fibrillation documented for at least six months before admission. Cardiomegaly was determined by the chest *x*-ray film, and was defined as a cardiothoracic ratio of greater than 50%. Haemodynamic studies were performed by methods and criteria previously published.[5] Single plane ventriculography was performed in the 40° right anterior oblique projection. Significant coronary heart disease was defined as luminal narrowing of more than 50% on selective arteriography. The presence of mitral regurgitation was assessed during beats which were not ventricular premature contractions.

Patients with atrial fibrillation and significant coronary heart disease were compared with a control group of 25 patients with coronary artery disease in sinus rhythm. These were selected randomly from our records but were matched for age and sex. The clinical, haemodynamic, and angiographic features of these two groups were compared using χ^2 or Fisher's exact test for qualitative data and Student's t test for quantitative data. Significance is defined as a p value of less than 0·05.

Results

Retrospective review of 1176 patients with documented significant coronary artery disease by angiography showed 10 (0·8%) patients with chronic atrial fibrillation. Their ages ranged from 43 to 67 years. The ages of patients with sinus rhythm ranged from 46 to 73 years. There were no significant age or sex differences between the two groups. Table 1

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Table 1 *Characterisation of coronary heart disease associated with atrial fibrillation*

Clinical status	*Patients with atrial fibrillation (N=10)*	*Control subjects (N=25)*	*p**
Congestive heart failure	7 (70%)	2 (8%)	<0·001
Third heart sound	5 (50%)	0 (0%)	<0·001
Normal electrocardiogram	1 (10%)	14 (56%)	<0·005
Anterior infarction on electrocardiogram	6 (60%)	1 (4%)	<0·002
Cardiomegaly on chest *x*-ray film	10 (100%)	3 (12%)	<0·001
Diabetes mellitus	4 (40%)	7 (28%)	NS
History hypertension	5 (50%)	9 (36%)	NS
Systolic murmur	4 (40%)	6 (24%)	NS
Smoking history	4 (40%)	10 (40%)	NS

*Fisher's exact test.

details the clinical characteristics of the two groups. There were highly significant correlations between atrial fibrillation and congestive heart failure ($p<0·001$), the presence of a third heart sound ($p<0·001$), and cardiomegaly ($p<0·001$). Anterior myocardial infarction was present in 6 of the 10 patients with atrial fibrillation compared with two of the 25 patients with sinus rhythm ($p<0·002$), while the electrocardiogram was normal in only one of the former compared with 14 of the latter ($p<0·005$). There was no significant difference between the two groups in the duration of symptoms, or in the presence of hypertension, diabetes mellitus, or a systolic murmur. The haemodynamic and angiographic findings are summarised in Table 2. No significant differences were found in the severity or anatomical distribution of coronary arterial obstruction. Analysis of left ventricular contractile patterns disclosed that this was normal in 10 (40%) of the control group with sinus rhythm but in none of those with atrial fibrillation ($p<0·005$). Furthermore, the latter had a significantly decreased ejection fraction compared with control subjects (0·30 vs 0·66, $p<0·001$) (Fig.). There was an increase in both the mean left ventricular end-diastolic pressure (19±9·9 mmHg vs 16±7·0 mmHg, $p<0·01$) and the mean left ventricular end-diastolic volume index (95±34 ml/m^2 vs 59±28 ml/m^2, $p<0·005$) in the patients with atrial fibrillation, in whom mild mitral regurgitation with opacification of the left atrium during one or two beats was statistically more frequent (three vs five patients).

Table 2 *Haemodynamic and angiographic characterisation of coronary heart disease associated with atrial fibrillation*

Catheterisation data	*Patients with atrial fibrillation (N=10)*	*Control subjects (N=25)*	*p value*
Single vessel disease	3 (30%)	8 (32%)	NS
Double vessel disease	2 (20%)	9 (36%)	NS
Triple vessel disease	5 (50%)	8 (32%)	NS
Contractile pattern normal	0 (0%)	10 (40%)	<0·005
Asynergy			
Inferior	3 (30%)	6 (24%)	NS
Anteroapical	4 (40%)	7 (28%)	NS
General hypokinesia	3 (30%)	2 (8%)	NS
Mitral regurgitation	5 (50%)	3 (12%)	<0·05
LVEDP (mean) (mmHg)	19±9·9	16±7·0	<0·01
LVEDV index (mean) (ml/m)	95±34	59±28	<0·005
Ejection fraction	0·30±0·17	0·66±0·18	<0·001

LVEDP, left ventricular end-diastolic pressure (mmHg); LVEDV, left ventricular end-diastolic volume/body surface area (ml/m).

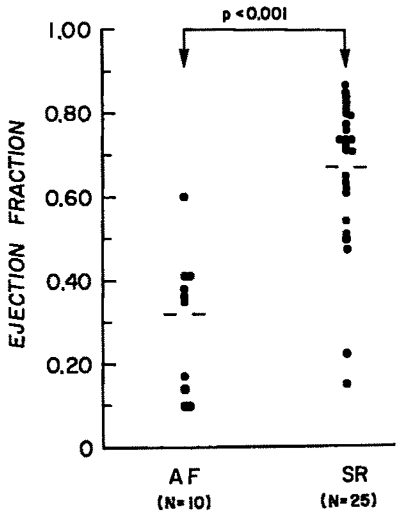

Fig. *Comparison of left ventricular ejection fraction in patients with atrial fibrillation and control group with normal sinus rhythm.*

Discussion

Although atrial fibrillation in the course of acute myocardial infarction has been extensively studied,[1-9] our observations on the clinical and angiographic significance in chronic coronary heart disease have not been previously described. Our data demonstrate that atrial fibrillation in patients with chronic coronary heart disease is associated with significant impairment of left ventricular function, mitral regurgitation, and left ventricular contraction abnormalities.

In the acute setting, considerable debate still exists concerning the prognostic significance of this arrhythmia. Several authors[6-8] have found an increased mortality in patients with atrial fibrillation during acute myocardial infarction. Cristal *et al.*[3] have emphasised that a greater overall mortality occurred when this rhythm was associated with acute anterior infarction. Others, however, have not shown an enhanced mortality.[2 9-11] A variety of mechanisms leading to the genesis of atrial fibrillation in acute infarction has been proposed which includes left ventricular failure, atrial infarction, pericarditis, and endogenous catecholamine release.[1 6] It is of interest that while the incidence of atrial fibrillation in acute myocardial infarction is approximately 10%,[7-9 12] our study population of 1176 patients with coronary artery disease discloses an incidence of 0·08%. Thus, while this rhythm is relatively frequent in the acute infarction period, it probably results from transient causes since persistent atrial fibrillation in chronic coronary artery disease is uncommon.

Whatever the mechanism of initiation of atrial fibrillation in patients with coronary artery disease, the absence of concerted atrial systole reduces effective cardiac output by 5 to 15%.[13] It is well known that in patients with impaired left ventricular function, the advent of atrial fibrillation results in prompt clinical deterioration.[13] Our findings that atrial fibrillation is associated with myocardial infarction and seriously impaired left ventricular function suggest that the latter may cause the arrhythmia by increasing left atrial pressure and, thus, by a vicious circle mechanism, lead to further deterioration of myocardial performance. The findings of heart failure and left ventricular haemodynamic deterioration are not related to differences in coronary anatomy since the extent and the distribution of angiographic lesions were similar in the group with atrial fibrillation and the control group. Another function of effective atrial contraction is the role in mitral and tricuspid valve closure in preventing ventriculoatrial regurgitation.[13 14] This may be an additional explanation of the finding of mitral regurgitation in 50% of the group with atrial fibrillation compared with 12% of the patients with sinus rhythm ($p<0{\cdot}05$).

While an irregular heart rate may result in a variable position of the mitral leaflets in presystole with resulting valvular regurgitation, we do not believe that atrial fibrillation is the sole cause of this. Mitral regurgitation is frequently associated with left ventricular dilatation, contractile abnormalities, and papillary muscle dysfunction, all of which were found in our patients with atrial fibrillation.[14-16] Therefore, atrial fibrillation and mitral regurgitation may coexist in the setting of advanced coronary heart disease.

In summary, atrial fibrillation in chronic coronary heart disease is unusual. The presence of this arrhythmia is, however, correlated with impairment of haemodynamic function, mitral regurgitation, and abnormalities of left ventricular contraction. It is, thus, a useful marker of extensive myocardial dysfunction.

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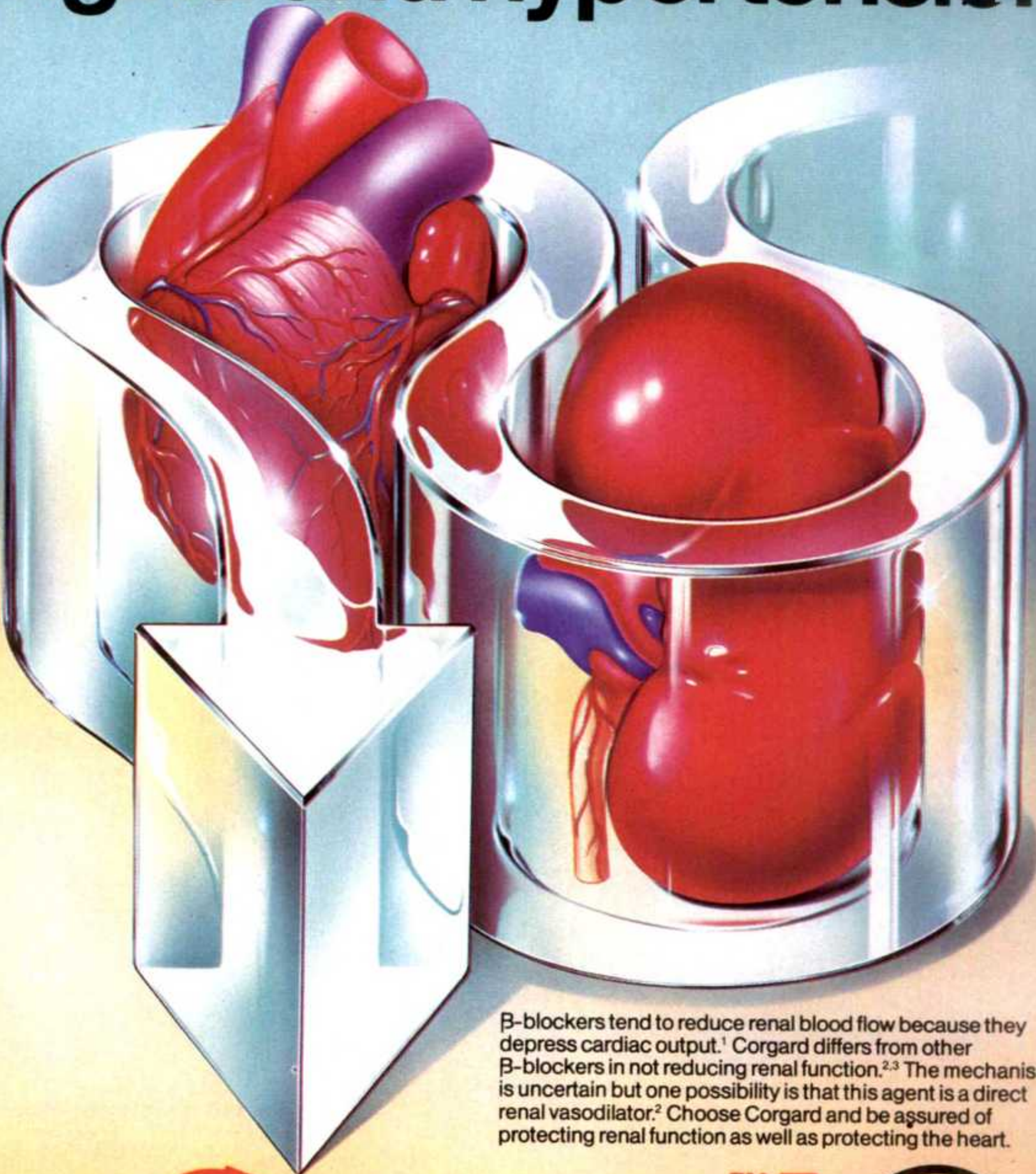

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Long-term control of reciprocating paroxysmal tachycardia by ventricular pacing in a case of Wolff-Parkinson-White syndrome

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SUMMARY A patient is described with a complex electrocardiographic pattern, including pre-excitation, grade 1 atrioventricular block, reciprocal rhythm of atrial origin, and frequent attacks of reciprocating tachycardia at a rate of about 135 beats per minute. Long-term control of these attacks was obtained by synchronous ventricular pacing at 80 beats a minute, which was below the rate during the attacks of tachycardia and above the spontaneous heart rate between the attacks.

Pacemaker treatment has been used for different purposes in cases of paroxysmal tachycardia. Firstly, magnetically induced atrial or ventricular asynchronous pacing has been successfully used in terminating attacks of paroxysmal tachycardia of both ventricular and supraventricular origin. Secondly, prophylactic pacing has been used in order to avoid severe sinus bradycardia and atrioventricular block when large doses of antiarrhythmic drugs are required to prevent such attacks. Thirdly, long-term atrial or ventricular pacing at a rate above the spontaneous heart rate but below the rate of the tachycardia has been described. This technique has been used mainly for ventricular tachycardia but also in a few cases of supraventricular tachycardia.[1 2] The present report concerns a patient successfully treated for paroxysmal reciprocating tachycardia of atrial origin by means of ventricular pacing below the rate of the tachycardia. Furthermore, this patient had alternating atrioventricular block and pre-excitation, suggesting a complex defect in the atrioventricular connection.

Case report

The patient was a 32 year old man previously healthy apart from his heart disease. His father had had a myocardial infarction when he was 55 years old. His mother suffered from diabetes, but was otherwise well. He had one brother who was healthy. The patient had a physically light office job and performed mild exercise in the holidays without any particular shortness of breath. He had never had chest pain.

Since puberty he had suffered from troublesome daily attacks of palpitation. After fainting at 16 years of age, auscultation disclosed an irregular heart rhythm, with paroxysmal attacks of tachycardia at a rate of about 140, but no other abnormality. The chest *x*-ray film showed moderate cardiomegaly without enlargement of any specific heart chamber. The blood pressure was 115/70 mmHg. The electrocardiogram was similar to those recorded later and is described below. A coronary angiogram was normal. On exercise testing the patient managed 900 kpm for four minutes and then gave up because of shortness of breath. The attacks of reciprocating tachycardia increased in duration and frequency during exercise. He was first treated with verapamil 80 mg three times a day which was later replaced by digitoxin 0·1 mg once a day without improvement.

When first seen at our hospital at the age of 32 years his condition had been unchanged for many years. The clinical, electrocardiographic and exercise findings were unaltered. Coronary arteriography was not repeated. Echocardiography showed moderate enlargement of the left atrium and left ventricle. There was reduced movement of the walls of the latter, which were of normal thickness. These findings suggested some form of cardiomyopathy. There were no valvular lesions. The electrocardiogram showed a complex variable picture.

(1) Sinus rhythm with a prolonged PR interval (0·22–0·28 s) (Fig. 1).

(2) Pre-excitation with a PR interval of 0·10 s, a widened QRS complex, and slurred delta waves (Fig. 2).

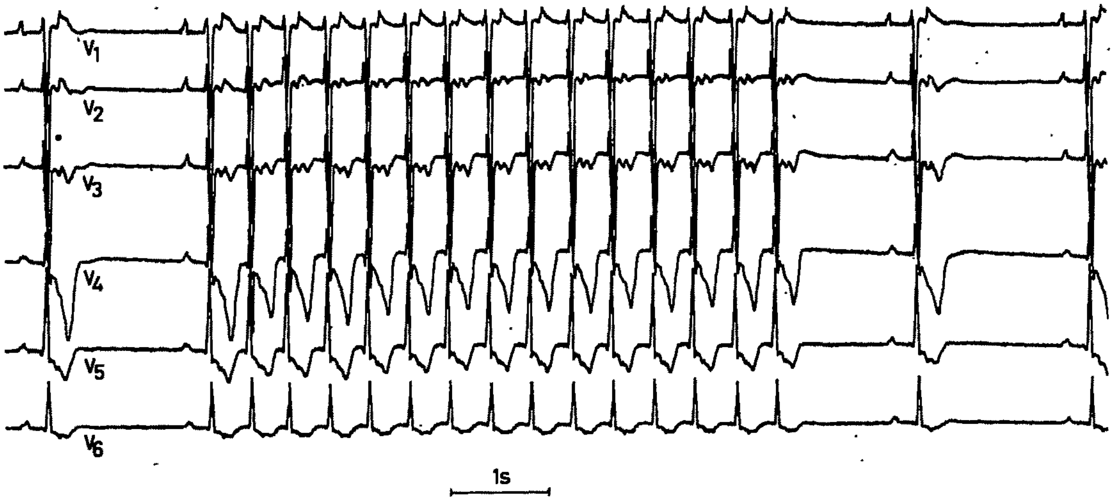

Fig. 1 *Reciprocating tachycardia. Rate 135/minute. On the right of the figure there is bradycardia, at 54/minute, because of reciprocal rhythm of atrial origin. The reciprocal atrial activation discharges and resets the sinus node. PR prolonged at 0·28 s (trace recorded at 25 mm/s).*

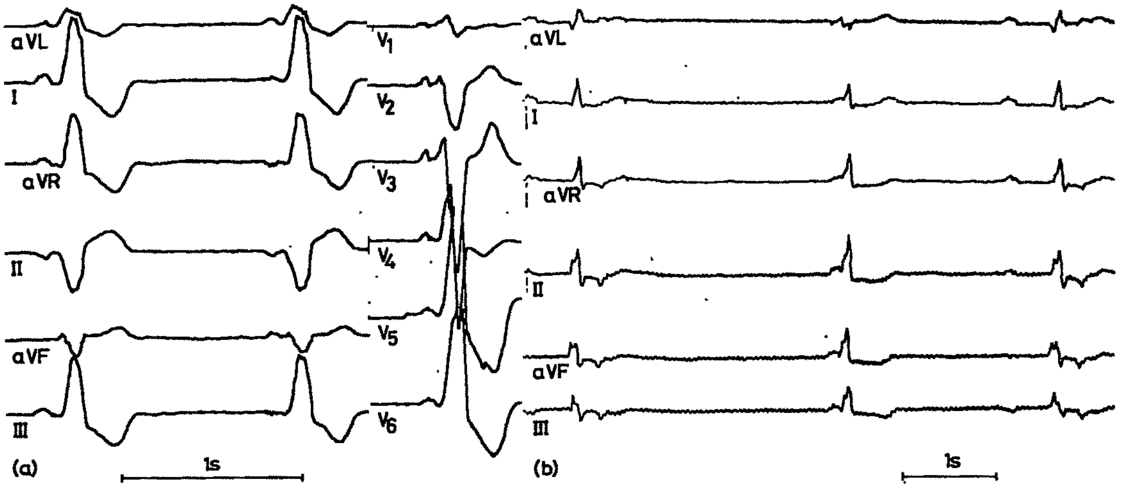

Fig. 2 *(a) Shows pre-excitation with a short PR interval and widened QRS complex with slurred delta waves (trace recorded at 50 mm/s). (b) Illustrates escape capture bigeminy (trace recorded at 25 mm/s).*

(3) Reciprocal rhythm of atrial origin with a P-QRS-P′ configuration (Fig. 1). The occurrence of P′ was strongly positively correlated with the length of the preceding PR interval. Retrograde conduction to the atria required a PR interval of at least 0·26 s. The RP′ interval was fixed at 0·17 s and P′ was superimposed upon the ST segment. The retrogradely conducted impulse P′, which had a frontal plane vector of about −90°, discharged the sinoatrial node and thereby postponed the ensuing cycle. This resulted in long periods of bradycardia at a rate of about 50 beats a minute.

(4) The bradycardia described above was sometimes replaced by escape capture bigeminy because of the escape of an idionodal or high ventricular pacemaker (Fig. 2). This escape beat was occasionally preceded by a non-conducted sinus impulse.

(5) Attacks of reciprocating paroxysmal tachycardia at about 135/minute (Fig. 1 and 3) which always began with a sinus P wave after a long RR interval (1·5 to 1·7 s), caused by the discharge and resetting of the sinus pacemaker by reciprocal retrograde atrial activation. The sinus P wave beginning the paroxysm was conducted with first degree atrioventricular block (PR

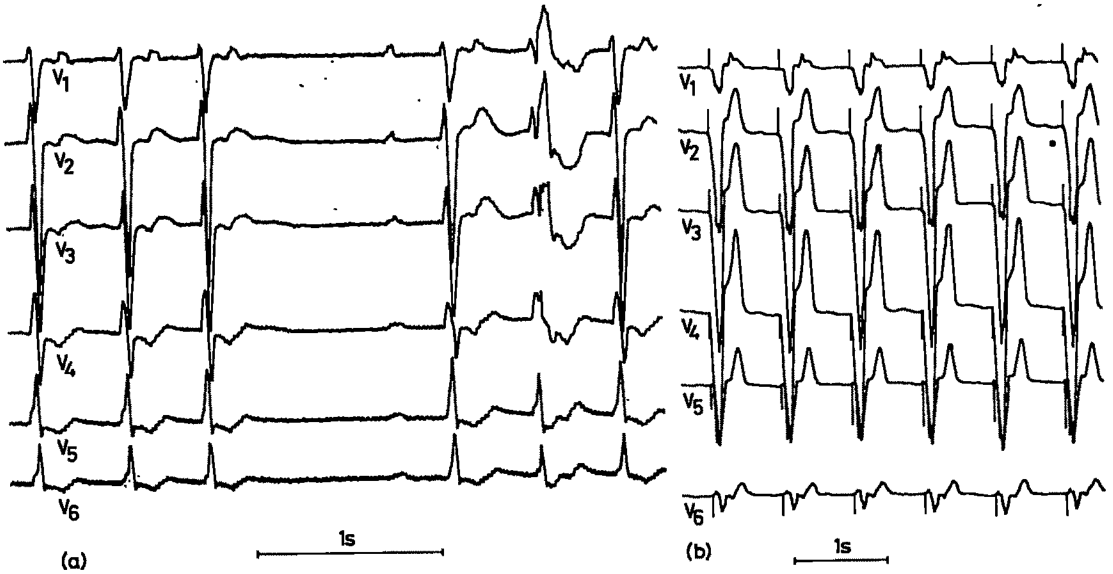

Fig. 3 *(a) Reciprocating tachycardia. Note right bundle-branch block caused by phasic aberrant conduction of the second beat in the last paroxysm of tachycardia (trace recorded at 50 mm/s). (b) Ventricular pacing at a rate of 80. Note retrograde atrial activation (trace recorded at 25 mm/s).*

interval 0·26 to 0·28 s). The electrocardiogram was consistent with a re-entry tachycardia probably using an abnormal conduction pathway between atria and ventricles. The existence of such a condition can be deduced both from the pre-excitation as well as from the retrograde atrial activation previously described. During tachycardia the RP′ interval was 0·17 s and P′R 0·28 s. All attacks of paroxysmal tachycardia were terminated by a P′, indicating retrograde atrial activation.

(6) The second beat in the paroxysms often had a right bundle-branch block configuration, reflecting phasic aberrant ventricular conduction because of the long preceding RR interval (Fig. 3).

(7) A few unifocal ventricular premature beats were found only after long preceding RR intervals, indicating secondary ventricular extrasystoles (Fig. 3).

The electrocardiographic findings suggested a trial of pacing might be effective. The long RR interval invariably preceding the attacks of tachycardia could be suspected of being of pathogenetic significance for these attacks, in which case pacing would suppress them. Furthermore, antiarrhythmic drugs in high doses could be used more safely during pacing.' Because of the intermittent atrioventricular block we preferred ventricular rather than atrial pacing and placed a temporary pacemaker electrode in the right ventricle. Before pacing, a 24 hour recording of the electrocardiogram showed that the paroxysms of reciprocating tachycardia were present 10% of the time and the patient experienced palpitation. At a pacing rate of 70/minute the frequency and duration of the paroxysms diminished conspicuously and at a rate of 80 they disappeared totally at rest. This was confirmed with 16 hours of continuous monitoring. The heart rate of 80 was not accompanied by palpitation and the patient felt well. The electrocardiogram showed pacemaker-induced ventricular activation with retrograde atrial activation (Fig. 3). During exertion the paroxysms occasionally returned. When the pacing rate was increased their frequency fell but the patient then noted palpitation at rest.

When the pacing impulse by asynchronous pacing appeared in a critical phase of the re-entry circuit in reciprocating tachycardia it should have stopped the tachycardia, but this did not happen and so we therefore ultimately fitted the patient with a permanent synchronous (QRS inhibited) pacemaker (Microlith), with a basic rate of 80/minute. The patient was also treated with metoprolol (100 mg) twice a day and digitoxin 0·25 mg daily, and he remained well. Four hours ambulatory electrocardiographic recording disclosed only paced rhythm. During the first 30 Watt load of an exercise test paced rhythm persisted; at 60 Watts there was alternation between paced and sinus rhythm; at 90 and 120 Watts there was sinus rhythm only with a maximum rate of 150/minute.

Discussion

The combination of pre-excitation, reciprocal rhythm of atrial origin, and reciprocating tachycardia in the same patient fits well with the assumption of an anomalous atrioventricular communication. The combination is rare and we have found only one previously described patient with the combination.[3] This patient had an electrocardiographic picture very similar to our patient and was subjected by Schamroth to a detailed electrocardiographic analysis.[3] Similar cases have also been described by Krikler *et al.*[4 5] The reciprocal rhythm of atrial origin and reciprocating tachycardia are readily explained by a differential refractoriness between the normal and the anomalous pathway. It is thus known that the anomalous atrioventricular bypass in the Wolff-Parkinson-White syndrome usually has a longer refractory period but a faster conduction rate than the normal atrioventricular communication.[6] A critically timed impulse may therefore penetrate the normal communication and return to the atria through the abnormal communication, thereby creating a circus movement. The relation between a long PR interval and reciprocal atrial activation in our patient is best explained by an upper common pathway requiring a relatively long reciprocal time to recover. On the other hand, the presence of grade 1 atrioventricular block and pre-excitation in the same electrocardiographic tracing points to alternative pathways within the atrioventricular node. One pathway may have normal conduction velocity and connections with the abnormal atrioventricular communication, thereby creating the typical fusion ventricular activation complex of pre-excitation. Another pathway may have a slowed conduction and no connection with the abnormal atrioventricular communication, thereby creating grade 1 atrioventricular block with a narrow QRS complex. The complex labyrinthine structure of the atrioventricular node[7] may form the anatomico-physiological basis for such different pathways.

The paroxysmal re-entry tachycardia in the Wolff-Parkinson-White syndrome is seldom so troublesome that permanent pacing is justified. A similar case was described with successful dual demand pacemaking designed to switch into the fixed rate mode (at 70 beats a minute) when the cardiac rate exceeded 150.[5] The findings in our patient indicate that synchronous ventricular pacing at a relatively high basic rate (80 beats a minute) may be valuable in preventing paroxysms of re-entry tachycardia. The retrograde P′ wave during pacing has an identical appearance to the P′ during reciprocal rhythm of atrial origin. This is a very strong argument that P′ is not an ectopic premature atrial beat. The prevention of paroxysmal supraventricular tachycardia by pacing at a rate below that of the tachycardia but above that of the heart rate between the paroxysms has previously been described by Moss and Rivers[2] and Sowton *et al.*[8] and is of considerable theoretical and practical interest. The electrophysiological explanation of the good results in our case seems to be, at least partly, the use of the anomalous atrioventricular bypass in retrograde conduction of the pacing impulse. The non-refractory period of this pathway is probably too short to allow its participation in the re-entry circus movement of the reciprocating tachycardia. From a theoretical point of view such occupation of the anomalous pathway by retrogradely conducted pacing impulses indicates that artificial pacing may be of value in preventing attacks of tachycardia in patients with the Wolff-Parkinson-White syndrome.

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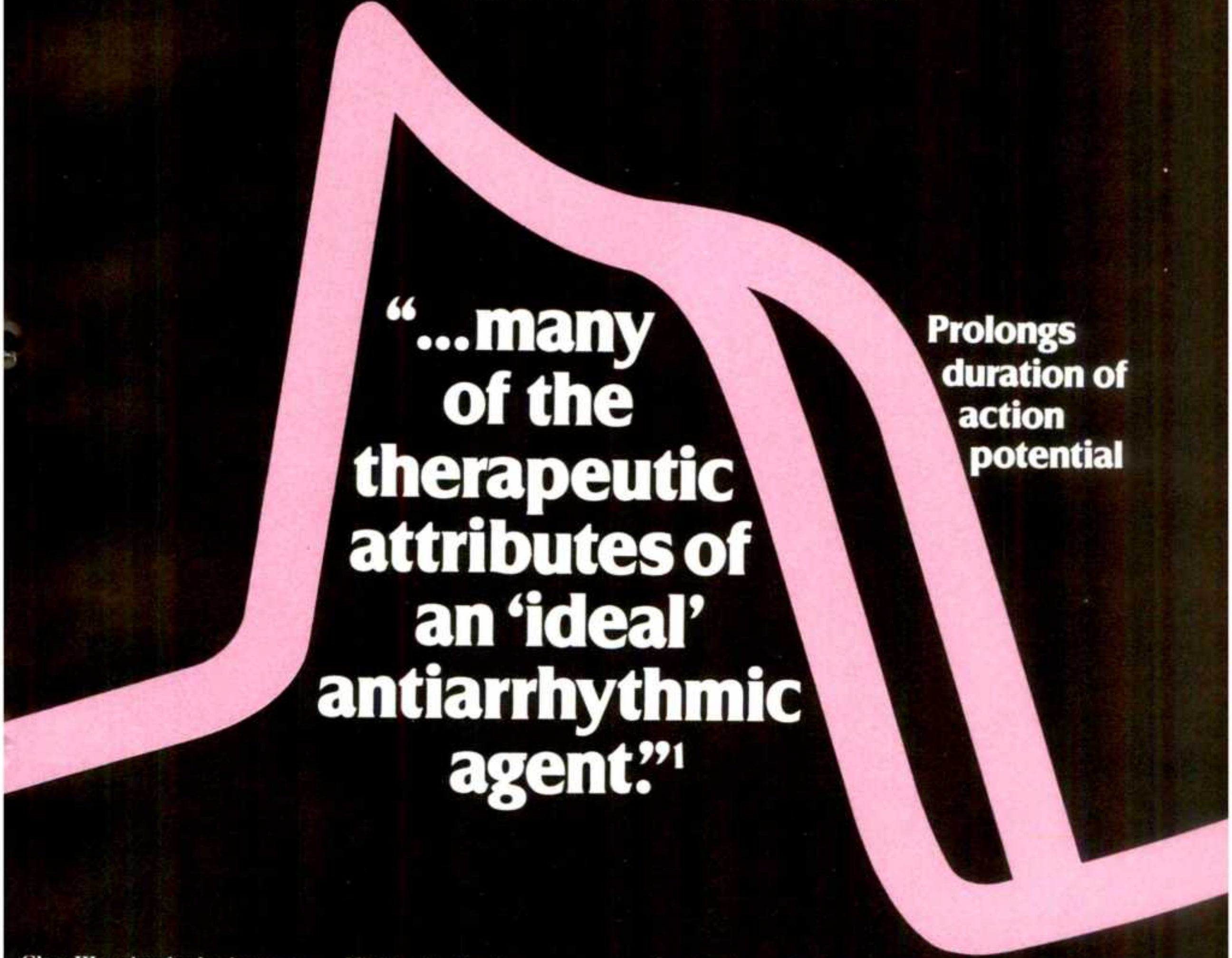

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1. Am J. Cardiol., (1977), 39, 446
2. Cordarone X Clinical & Technical Review, available on request.

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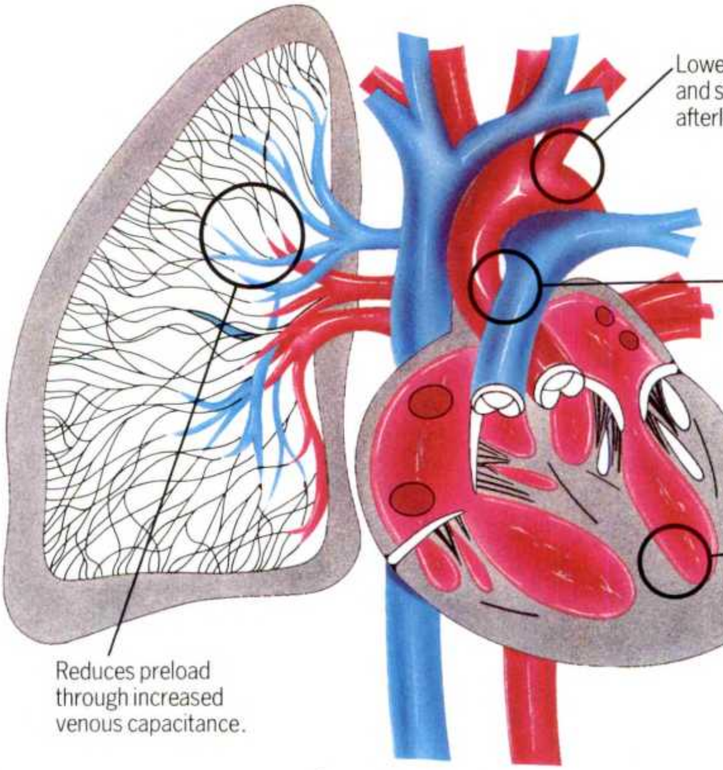

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Incessant junctional reciprocating tachycardia caused by dual atrioventricular nodal pathways and atrio-nodal bypass tract

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SUMMARY A case is described with clinical and electrocardiographic findings of incessant junctional reciprocating tachycardia. Electrophysiological study showed that longitudinal dissociation of the atrioventricular node into two pathways was responsible for the maintenance of the arrhythmia. The two intranodal pathways had different refractory periods but reciprocally related and overlapping conduction times (anterograde fast, retrograde slow, and vice versa). Induction and termination of the arrhythmia was related to the presence of a partial atrio-nodal bypass tract.

Atrioventricular re-entry is the most common mechanism of paroxysmal sustained supraventricular tachycardia in man.[1] Atrioventricular nodal re-entry is the result of a functional or anatomical dissociation of the atrioventricular node into two pathways with different conduction times and refractory periods.[2-4] In the usual type of atrioventricular nodal re-entry, the slow pathway is used for anterograde conduction and the fast pathway for retrograde propagation of the re-entrant impulse.[3] Induction of atrioventricular nodal re-entry is dependent on the achievement of a critical atrioventricular nodal delay (AH interval).[4] Wu *et al.*[5] described an unusual type of atrioventricular nodal re-entry in which there is an intranodal anterograde fast and a retrograde slow pathway. They also showed that both types of atrioventricular nodal re-entry, usual and unusual, may be present in the same patient, that is the slow and fast pathways can be used in both anterograde and retrograde direction at different times.[5] Coumel *et al.*[6 7] described an incessant form of junctional reciprocating tachycardia in children. Induction of the incessant form of tachycardia is not dependent on a critical conduction delay but requires a critical atrial coupling interval or rate.[6 7] Similar observations have also been made in patients with the Wolff-Parkinson-White syndrome.[8 9]

We describe a case with clinical presentation of incessant junctional reciprocating tachycardia. Initiation of the supraventricular tachycardia was not dependent on critical atrioventricular conduction delay but required a critical atrial coupling interval or rate. The electrophysiological study suggested the presence of dual atrioventricular nodal pathways and a partial atrio-nodal bypass tract. The intranodal pathways (alpha and beta) had different refractory periods but overlapping conduction times.

Case report

A 56-year-old woman was admitted to the hospital because of a long standing history of palpitation (lasting from minutes to several days) and chest pain. The patient had a past history of hypertension. She had received propranolol and quinidine in the past without any improvement in her symptoms. Physical examination was normal. The chest *x*-ray film and M-mode echocardiogram showed nothing abnormal. The electrocardiogram during sinus rhythm showed left atrial abnormality and was otherwise normal. During supraventricular tachycardia the P waves preceded the QRS complexes with PR intervals of 0·16 s. The rate of the tachycardia was 140/min. Spontaneous initiation and termination of the tachycardia on rhythm strips was related to the occurrence of a premature atrial beat without significant lengthening of the PR interval.

The electrophysiological study was performed after informed consent was obtained. Electrode catheters were positioned under fluoroscopic control in the high right atrium, coronary sinus, and His bundle region. At the time of the study, the patient was in supraventricular tachycardia. During the initial intracardiac recording three different types of supraventricular tachycardia with identical retrograde activation sequence and cycle length, but with varying anterograde (A_e-H) conduction times, were observed (Fig. 1). Tachycardia number one had an A_e-H interval of 240 ms and an H-A_e of 220 ms. The H-A_e/A_e-H ratio was 1:1·1 (Fig. 1A). Tachycardia number two had an A_e-H interval of 190 ms and an H-A_e of 270 ms. The H-A_e/A_e-H ratio was 1:0·7 (Fig. 1B). Tachycardia number three had an A_e-H interval of 140 ms and an H_e-A of 320 ms. The H-A_e/A_e-H ratio was 1:0·4 (Fig. 1C). The three types of tachycardia were sustained; transition from one type of tachycardia to another was observed on the monitor to be abrupt, and could not be recorded. Coupled atrial

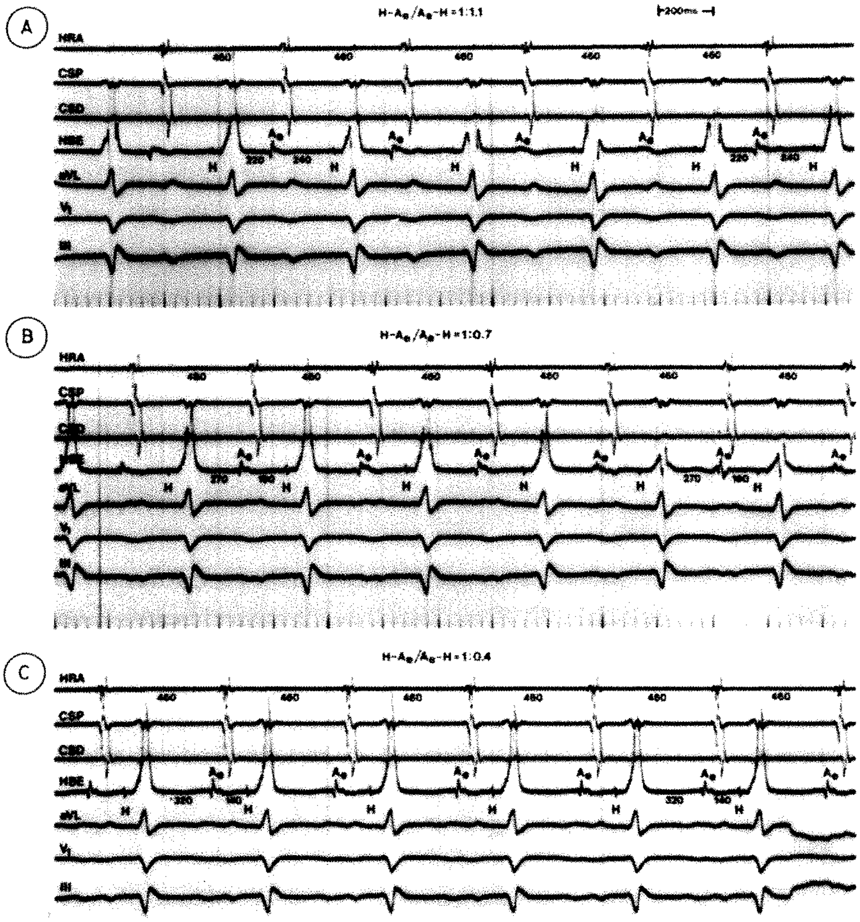


Fig. 1 *Spontaneous paroxysmal supraventricular tachycardia (PSVT). Electrocardiographic leads aVL, V1, III, and intracardiac high right atrial (HRA), proximal coronary sinus (CSP), distal coronary sinus (CSD), His bundle (HBE) electrograms are shown. A_e represents the atrial echo beat and H the His bundle electrogram. The paper speed in this and subsequent illustrations is 100 mm/s and the time lines are at 40 ms. Measurements are expressed in ms. (A) PSVT No. 1. There is low to high atrial depolarisation sequence (HBE→CSP→HRA→CSD) the cycle length of the tachycardia is 460 ms, with H-A_e of 220 ms and A_e-H of 240 ms. The H-A_e/A_e-H ratio is 1:1·1. (B) PSVT No. 2. The atrial depolarisation sequence and cycle length of the tachycardia is identical to PSVT No. 1. The H-A_e however, is 270 ms and A_e-H is 190 ms and the ratio is 1:0·7. (C) PSVT No. 3. The atrial depolarisation sequence and cycle length of tachycardia are identical to PSVT No. 1 and 2. The H-A_e, however, is 320 ms and the A_e-H is 140 ms. The H-A_e/A_e-H ratio is 1:0·4.*

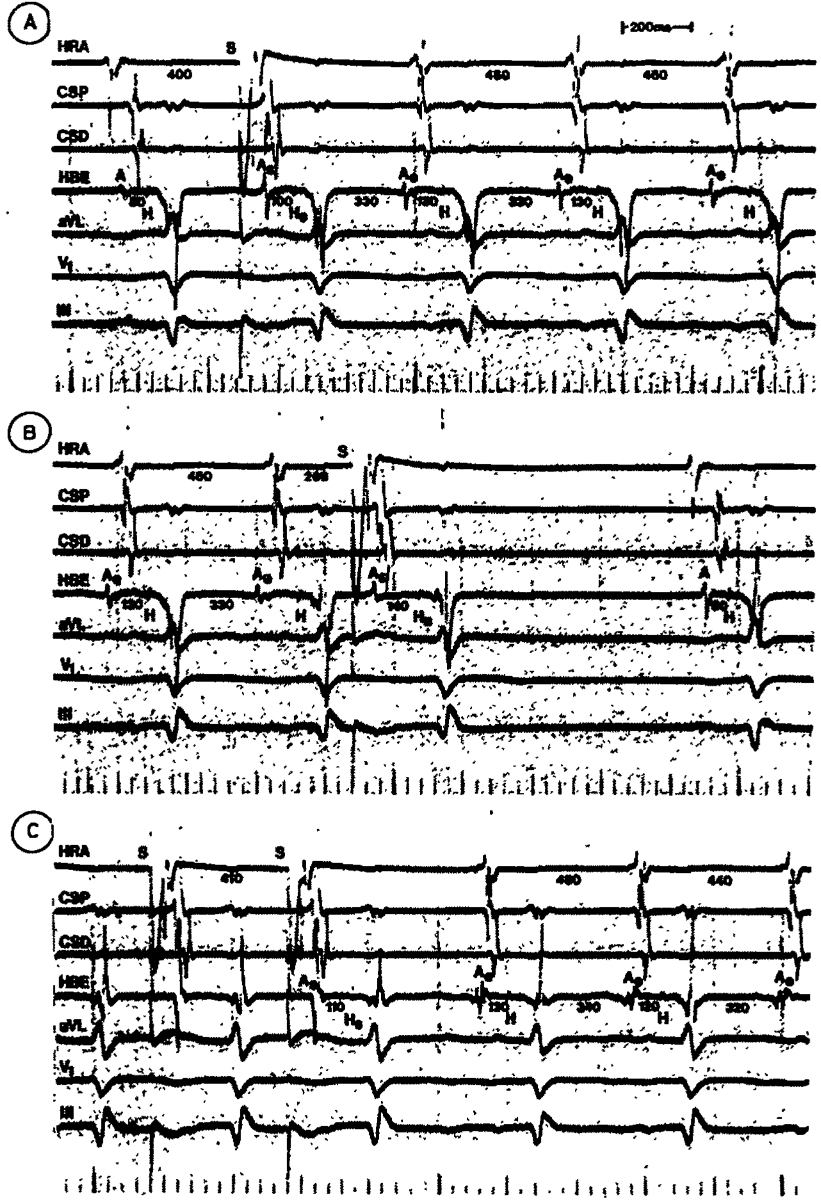


Fig. 2 *Initiation and termination of PSVT. Abbreviations similar to Fig. 1. S represents the pacing stimulus, A_s the atrial depolarisation, and H_s the His bundle depolarisation in response to the atrial extrastimulus. (A) During sinus rhythm, PSVT is induced with a single atrial extrastimulus (S) at a coupling interval of 400 ms. During sinus rhythm the AH interval is 80 ms; the A_s-H_s interval is 100 ms. The cycle length of the tachycardia is 460 ms, with an H-A_e and A_e-H of 330 ms and 130 ms, respectively. (B) A premature atrial impulse at a coupling interval of 260 ms terminates the PSVT by blocking in the retrograde pathway. Only slight prolongation of the A_s-H_s interval (140 ms) compared with the preceding A_e-H interval (130 ms) is seen. (C) Atrial pacing at a cycle length of 410 ms initiates the arrhythmia.*

pacing during tachycardia number three showed reproducible termination of the arrhythmia at a coupling of 260 ms (Fig. 2B). Initiation of tachycardia number three was dependent on a critical atrial coupling interval (Fig. 2A) or atrial paced cycle length (Fig. 2C). Coupled atrial pacing during tachycardia number three induced only minimal lengthening of the atrioventricular nodal conduction times (A_s-H_s) of the premature impulse (Fig. 3A, B, and C). In contrast, lengthening of retrograde conduction time (H_s-A_e) was observed, with increasing prematurity of the atrial impulse (Fig. 3A, B, and C). The plot of anterograde conduction time during coupled atrial pacing (A_s-H_s) and during supraventricular tachycardia (A_e-H) against the atrial coupling interval (H-A_s) and the retrograde conduction time (H-A_e) is shown in Fig. 3C. There is a distinct difference in anterograde conduction times at close coupling intervals. Specifically, at H-A_s and H-A_e intervals of 220 ms the anterograde conduction time during tachycardia (A_e-H) measured 240 ms (Fig. 1A, Fig. 3C), and during coupled atrial pacing (A_s-H_s) it was 140 ms (Fig. 3B and C).

During sinus rhythm the basic conduction intervals were as follows: PA was 30 ms, AH was 80 ms, and the HV was 40 ms. During coupled atrial pacing the atrioventricular nodal conduction curves (A_1A_2-H_1H_2) were continuous. During right ventricular pacing no ventriculoatrial conduction was present. The patient was discharged on amiodarone (600 mg/day) and remained free of symptoms a year later. The electrophysiological study was not repeated.

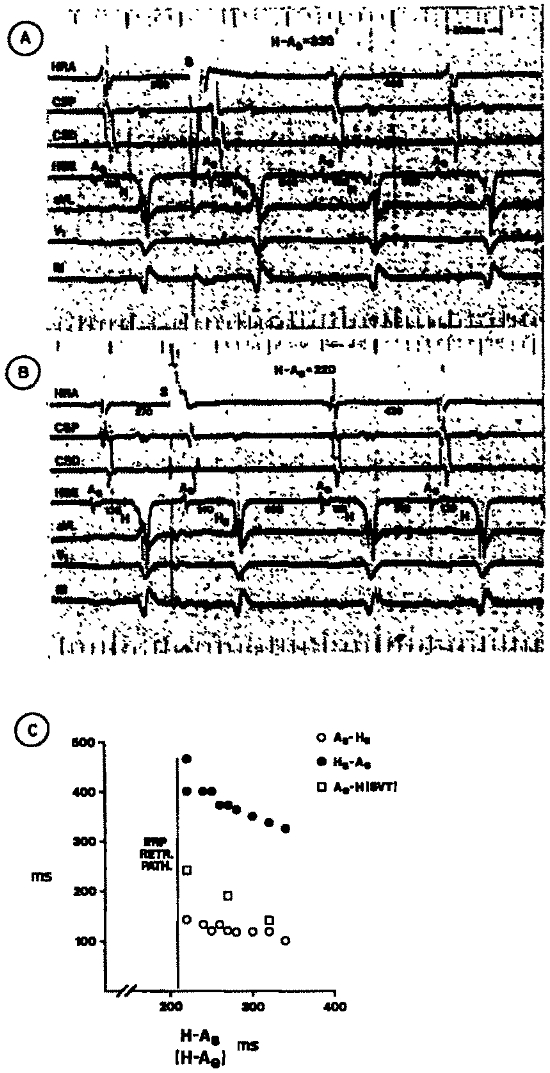
Comments

Induction and termination of the tachycardia in our patient with a single atrial extrastimulus suggest the presence of a re-entrant mechanism (Fig. 2).[1-7] The absence of ventriculoatrial conduction excludes the participation of a Kent bundle in the re-entry circuit.[1] The differentiation between atrial tachycardia, with different A_e-H and H-A_e intervals resulting from changes in autonomic tone, and atrioventricular nodal re-entrant tachycardia is more difficult; in our case the incessant form of the arrhythmia and the changes in AH intervals, however, which were abrupt and sustained, argue against atrial tachycardia and make atrioventricular nodal re-entry the most likely mechanism.[1 10]

We propose that the supraventricular tachycardia seen in our patient is the result of the presence of dual atrioventricular nodal pathways (alpha and beta) and, in addition, a partial atrionodal bypass tract. During sinus rhythm, the impulse propagates through the atrioventricular nodal pathways (alpha and beta) and through the bypass tract (Fig. 3D). An atrial premature beat or a critical increase in sinus rate results in an anterograde block in the beta pathway with conduction through the alpha pathway and the atrionodal bypass tract. Conduction through the bypass tract propagates with faster velocity than in the intranodal alpha pathway and engages the beta pathway in a retrograde direction. Retrograde conduction through the beta pathway occurs with sufficient delay to enable the alpha pathway to recover and complete the re-entrant circuit in an anterograde direction (Fig. 3D). Once the tachycardia is induced, the anterograde conduction occurs through the alpha pathway, the retrograde conduction through the beta pathway, and the depolarisation of the atria through the proximal common pathway (Fig. 3D). During tachycardia, the impulse conducts through the alpha pathway rather than the bypass tract because of its closer anatomical location to the retrogradely conducting beta pathway. Retrograde conduction occurs through the beta pathway rather than the bypass tract because of retrograde block in the bypass tract resulting from concealed anterograde conduction of the atrial echo beat (Fig. 3D). Termination of the arrhythmia is observed when a premature atrial beat at a critical coupling interval propagates through the bypass tract with a faster conduction velocity than through the alpha pathway, rendering the alpha and beta pathways refractory (Fig. 3D).

The electrophysiological characteristics of both anterograde and retrograde intranodal pathways (alpha and beta) need further discussion. The retrograde (beta) pathway showed a progressive lengthening of its conduction time (H_s-A_e) at decreasing H-A_s coupling intervals (Fig. 3C). The anterograde conduction time through the alpha pathway showed pronounced and reciprocal variations with the conduction time present in the beta pathway. In addition, unexpected differences were observed in anterograde conduction times between spontaneous tachycardia and coupled atrial pacing. In fact, as shown in Fig. 3C, at similar H-A_s and H-A_e intervals, the anterograde conduction time (A_e-H) during spontaneous tachycardia was considerably longer than the conduction time (A_s-H_s) observed during coupling atrial pacing. This finding suggests that the pathway used for anterograde conduction during supraventricular tachycardia (alpha pathway) was different from the pathway used when premature atrial extrastimuli were delivered (atrionodal bypass tract). The latter pathway failed to show significant increases in its conduction time at close coupling intervals (H-A_s), suggesting the presence of a partial atrionodal bypass tract. The absence of ventriculoatrial conduction in our case can be explained by a unidirectional block in the distal common pathway (Fig. 3D).

Akhtar *et al.*[11] showed that three patterns of parox-



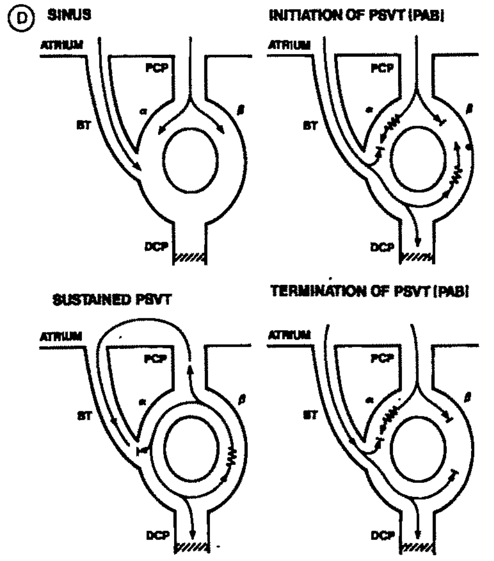


Fig. 3 *Atrial coupled pacing during PSVT. Abbreviations similar to Fig. 1. (A) During PSVT, a single premature atrial stimulus is delivered at a coupling interval of 360 ms. The coupling interval to the preceding H is 330 ms. The anterograde conduction time of the premature impulse (*A_s*-*H_e*) is shorter (120 ms) than the anterograde conduction time (*A_c*-H) during the PSVT (130 ms). (B) The coupling interval of the premature atrial impulse is decreased (270 ms). The H-*A_s* interval measures 220 ms; a minimal prolongation of the *A_s*-*H_s* interval is observed (140 ms). (C) The anterograde conduction time of the premature atrial impulse (*A_s*-*H_e*), the retrograde conduction time of the resulting echo beat (*H_s*-*A_e*), and the anterograde conduction time during PSVT (*A_c*-H) are plotted against the atrial coupling interval (H-*A_e*). *H_s*-*A_c* shows the expected lengthening with increasing shortening of H-*A_s*. At equivalent H-*A_s* intervals (330 ms and 220 ms), the conduction through the anterograde pathway during PSVT (*A_c*-H) shows distinct prolongation when compared with the anterograde conduction during coupled atrial pacing (*A_s*-*H_e*). (D) Schematic representation of the proposed mechanism of the PSVT. PCP, proximal common pathway; BT, bypass tract; DCP, distal common pathway; PAB, premature atrial beat; Cross hatched areas, zone of retrograde block. See text for discussion.*

ysmal atrioventricular junctional tachycardia can be identified on the basis of the relation between retrograde and anterograde conduction intervals (H-A_e/A_e-H) and that these ratios could offer a simple and reproducible method for determining the site of re-entry during supraventricular tachycardia. They also concluded that the ratios are fairly constant and the intermediate relations are only seen during changes of the cycle length of the tachycardia.[11] The varying H-A_e/A_e-H ratios (1:1·1 to 1:0·4) during spontaneous tachycardia observed in our case demonstrate the limited usefulness of this classification.[11]

Wu *et al.*[5] described three patients with atrioventricular nodal re-entrant tachycardia in whom the fast pathway was used for anterograde and the slow pathway for retrograde conduction (unusual type of atrioventricular nodal re-entry). They also showed that the same pathways could be used in the opposite direction, that is the fast for retrograde and the slow for anterograde conduction (usual type of atrioventricular nodal re-entry).[5] Though in our case both usual and unusual type of atrioventricular nodal re-entry were observed, our electrophysiological findings differ from the observations of Wu *et al.*[5] The alpha pathway was always used for anterograde conduction and the beta pathway was always used for retrograde conduction. There was a reciprocal relation between the alpha and beta pathway conduction times, that is when one was slow the other was fast and vice versa. Thus, in the present report, the anterograde and retrograde intranodal pathways could not be classified as either "slow" or "fast". For this reason we labelled them as alpha and beta pathways, according to the original description of Moe *et al.*[2] The varying and reciprocal changes of the conduction times in the two intranodal pathways recorded in this case are interesting in that they have not previously been reported in man, but observed only in the experimental animal models.[12]

The presence of partial atrio-nodal bypass fibres has been suggested to explain the lack of AH interval prolongation observed during initiation of incessant junctional reciprocating tachycardia.[13] The postulated partial atrio-nodal bypass tract, however, could also have been an intranodal structure.[13] Our case provides electrophysiological evidence for the presence of a partial atrio-nodal bypass tract separate from the atrioventricular node.

Finally, the therapeutic implications of the described mechanism deserve further comments. In our case, the induction and the maintenance of the tachycardia were critically dependent on the presence of an atrio-nodal bypass tract and of dual atrioventricular nodal pathways, respectively. Either a "myocardial" or a "nodal" drug, affecting the electrophysiological properties of the bypass tract or of the atrioventricular node, might have been considered in combination or alone, as previously described.[8 9] Amiodarone has been proved to exert significant electrophysiological effects (slower conduction velocity, increased refractory periods) on both the accessory pathway and the atrioventricular node.[14 15] Amiodarone may be the drug of choice in cases where multiple re-entrant pathways are responsible for the occurrence of supraventricular tachycardia.

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Br Heart J 1982; 47: 619–20

Coarctation of the aorta in monozygotic twins

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SUMMARY Concordant coarctation of the aorta has been found in a pair of monozygotic twins. One of the twins had a vascular ring.

The aetiology of coarctation of the aorta is still largely unexplained, and investigations on familial occurrence have given conflicting results.[1–3]

Only 10 reports of coarctation of the aorta in monozygotic twins have been published. The lesion has shown discordance[1 4–9] in all but one[10] of the cases. In only three of these was there a concordant cardiovascular malformation: atrial septal defect,[5] hypoplasia of the aortic arch,[8] and Marfan's syndrome,[9] together with coarctation of the aorta in one of the twins.

In this communication we describe coarctation of the aorta in a monozygotic pair of twins: the second reported case with concordance, and the first case where coarctation was found alone in one of the twins and appeared with a vascular ring in the other.

Case report

From the time of birth (May 1963) the twin girls were regarded as being monozygotic. Sixteen years later this assumption was confirmed by blood type, plasma enzyme and tissue type investigations, and by chromosome marker investigations, using a fluorescent banding method (see Table).

The vascular anomalies were assessed by means of cardiac catheterisation and angiocardiography as well as by direct inspection of the thoracic aorta during operation.

The twin with coarctation and vascular ring malformation, twin S, measured 49 cm at birth and had surgery at the age of almost 1 year. At operation the trachea was decompressed by division of both the ligamentum arteriosum and the totally coarctated segment of the pretracheal anterior aortic arch. The post-tracheal segment of the vascular ring had the size and function of a normal aortic arch, continuing into the descending aorta. The patient has since developed normally.

The twin with the isolated coarctation, twin J, measured 44 cm at birth and had an operation when 16 years old. The coarctation was of the so-called postductal type and was treated with a bypass graft.

Both girls were seen three months after twin J's operation. The respective heights were 152·5 cm for S and 147·5 cm for J. After 20 minutes' rest the blood pressures taken on the right arm were, respectively, 135/66 mmHg for S and 136/64 mmHg for J, who had a pressure of 145/80 mmHg preoperatively.

Ophthalmological examination showed that J's retinal arteries were more tortuous than those of S.

Discussion

In our department, in addition to the two cases reported here, we have operated on 232 patients with coarctation of the aorta. Four of these came from two families, a boy and his aunt and a brother and sister. This observation only lends limited support to the suggestion of Simon *et al.*[3] that there is "a genetic contribution to the aetiology of this disorder".

It has long been accepted that overdevelopment of the upper part of the body is characteristic of coarctation of the aorta. One of our twins (J) had had her coarctation and high proximal blood pressure for 16 years and yet showed no difference in the build of the

Table *Genetic evidence of zygosity*

		Rhesus									*Le*	*Fy*	*Jk*				
	ABO	*C*	*c*	*D*	*E*	*e*	*MNS*	*P1*	*Lu*	*K*	*ab*	*ab*	*ab*	*Bf*	*C2*	*Glo*	*HLA*
Twin J:	A2	−	+	+	+	+	+−−	+	a−	−	−+	−+	+−	FS	1	1	A2, B7/A9, Bw39
Twin S:	A2	−	+	+	+	+	+−−	+	a−	−	−+	−+	+−	FS	1	1	A2, B7/A9, Bw39

The twins had identical QM banded karyotypes. Informative markers were found in the following chromosome numbers: 1, 3, 4, 9, 13, 14, 15, 16, 21, and 22.

trunk, neck, or head compared with the other. Furthermore, twin J had shorter lower limbs accounting for the difference in height between the two. The same observation has been made by Driver and Suckling.[5] This might indicate that the characteristic build in this condition is caused more by underdevelopment of the lower half of the body than by overdevelopment of the upper half.

The investigation on blood types, and enzyme and tissue types was performed at the Blood Bank and Tissue Typing Laboratory, Aarhus Kommunehospital; the chromosome analysis was done at the Institute of Human Genetics, Aarhus University, Aarhus, Denmark. I am grateful to both these laboratories for their collaboration.

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Notices

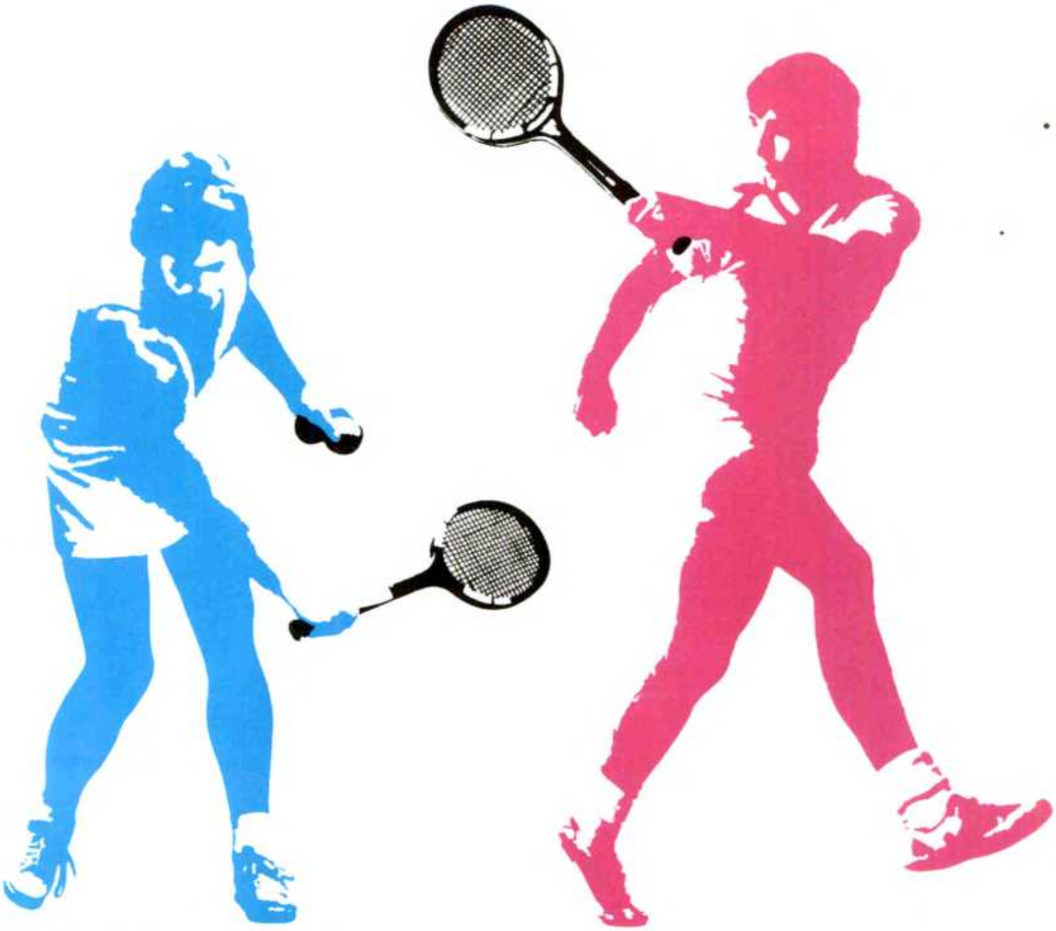
Subacute bacterial endocarditis

A survey is currently being carried out by the British Cardiac Society and the Medical Services Study Group of the Royal College of Physicians. Though improvement of dental prophylaxis is one objective, the survey is already yielding other valuable information. It is hoped that proformas will be received in respect of a high proportion of patients with subacute bacterial endocarditis in the British Isles seen during 1981 and 1982 and readers are asked to arrange for them to be submitted in respect of any cases that come to their notice. Proformas can be obtained from Sir Cyril Clarke, Medical Services Study Group, King's Fund Centre, 126 Albert Street, London NW1 7NF (tel. 01-267 6111, ext. 263) to whom they should be returned.

British Cardiac Society

The Autumn meeting will take place at Wembley on 6 and 7 December 1982 and the closing date for receipt of abstracts is 11 August 1982.

The Annual General Meeting for 1983 will take place in Bristol on 12 and 13 April, and the closing date for abstracts will be 4 January 1983. The Autumn Meeting will be held at Wembley on 21 and 22 November 1983, and the closing date for abstracts will be 28 July 1983.



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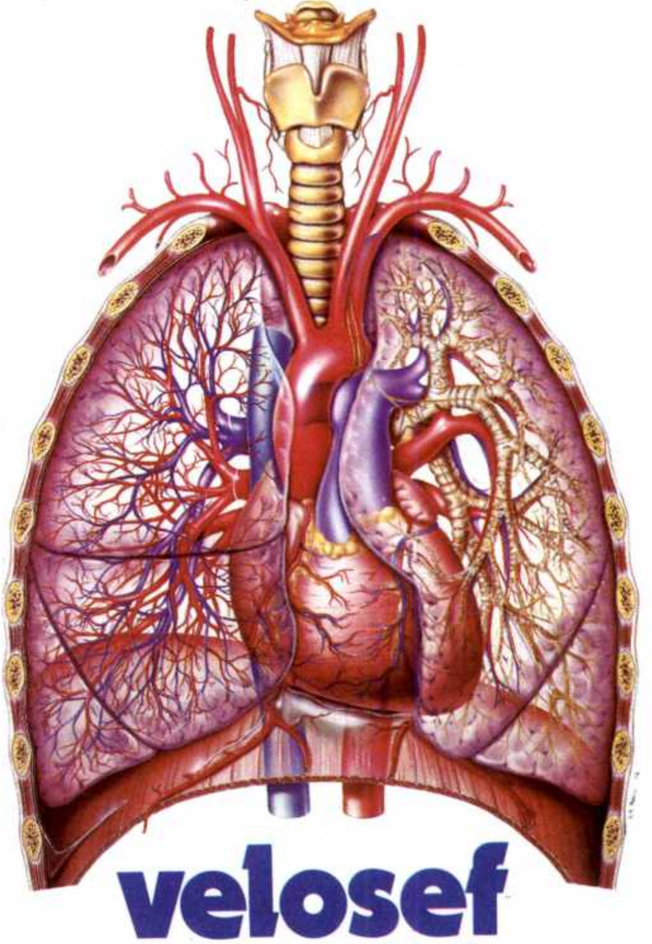

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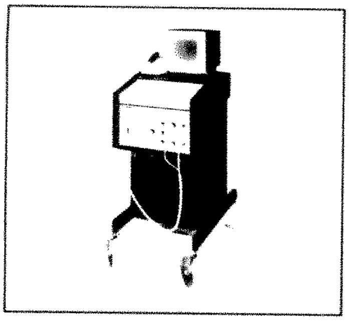

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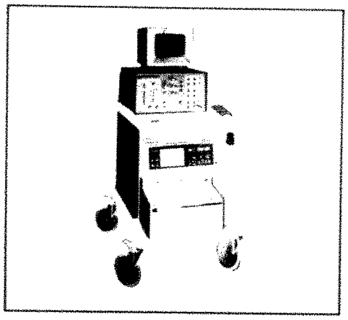

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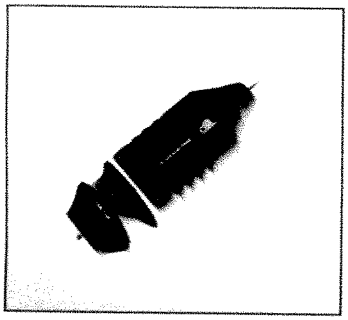

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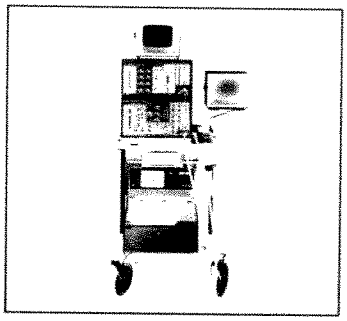

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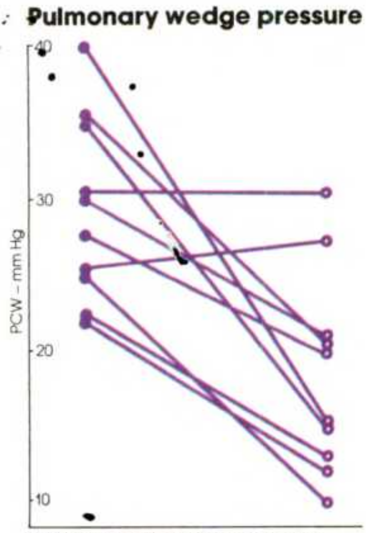
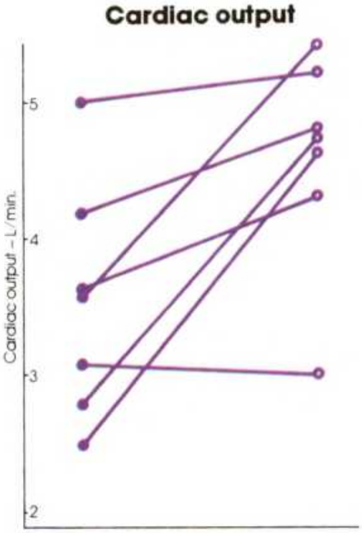
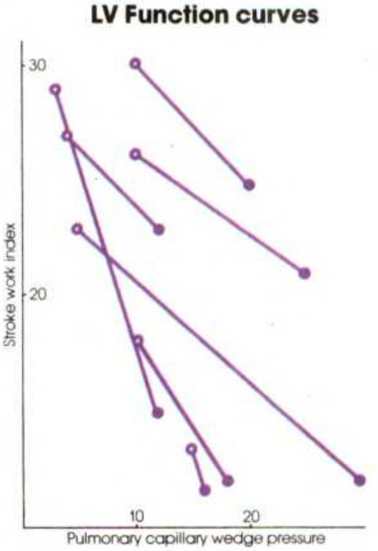


1. Effects of isosorbide dinitrate (Isoket) on pulmonary capillary wedge pressure.

PRIOR TO ISOKET ● ON "OPTIMAL" DOSE OF ISOKET ○



2. Effects of Isoket on cardiac output.



3. Effects of Isoket on left ventricular function curves.

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proven effective in heart failure

soket was administered i.v. in doses of 2-7 mg/hour to 10 patients suffering from extreme pump failure refractory to conventional therapy. Seven patients had severe coronary disease with recurrent infarctions; 5 receiving Isoket during an acute event and in 3 of them severe mitral regurgitation was documented. Three other patients received Isoket just prior to surgery with heart failure consequent to a ruptured ventricular septum, aortic insufficiency and a severely leaking mitral prosthesis.

Marked haemodynamic improvement during Isoket manifested by decrease of pulmonary wedge pressure (PWP) and systemic vascular resistance with increase of cardiac output was obtained in 7 of the 10 patients studied.

Mean arterial pressure was "markedly and favourably affected in those patients who had high initial pressures. The lower arterial pressures remained stable or even increased a little in two patients." Heart rate and the [illegible]myocardial gradient were not deleteriously affected.

Isoket also produced a complete abolition of the mitral regurgitation as evidenced by the disappearance of the giant 'V' wave on the PWP tracings.

The authors concluded that Isoket appears to be "a highly effective and rather safe drug in properly monitored patients with pump failure."[2]

A copy of this clinical paper, further information and a data sheet are available from:
Sanol Schwarz Pharmaceuticals Ltd.,
Th[illegible], 130 High Street, Chesham, Bucks. HP5 1EF Tel. (0494) 772071

Prescribing Information

Presentation Ampoules containing 10 mg Isosorbide dinitrate in 10 ml of colourless sterile isotonic saline. **Uses** Isoket is indicated in the treatment of unresponsive left ventricular failure secondary to acute myocardial infarction, unresponsive left ventricular failure of various aetiology and severe or unstable angina pectoris. Isosorbide dinitrate is a vasodilator, reducing the afterload and especially the preload of the heart. It influences the oxygen supply to ischaemic myocardium by causing the redistribution of blood flow along collateral channels and from epicardial to endocardial regions. It also reduces oxygen demand by increasing venous capacitance, causing pooling of blood in peripheral veins thereby reducing ventricular volume and heart wall distension. **Dosage and Administration** *Dosage* The dose employed must be adjusted according to the patient's response. In general, a dose of between 2 and 7 mg per hour is suitable, although doses as high as 10 mg per hour may be necessary. *Children* The safety and efficacy of Isoket has not yet been established in children. *Administration* Isoket is a concentrated solution and should never be injected directly. It should always be administered as an intravenous admixture with a suitable vehicle such as Sodium Chloride Injection B.P. or Dextrose Injection B.P. Prepared Isoket admixtures are always given by intravenous infusion or with the aid of an infusion pump. During administration, there should be close monitoring of the patient's blood pressure and pulse. Admixtures are prepared by exchanging the required volume of Isoket with an equal volume of the infusion vehicle. **For example, if a dose of 6 mg per hour is required, 50 ml of Isoket (equivalent to 5 x 10 ml ampoules) should be added to 450 ml of the infusion vehicle to give a final volume of 500 ml. This admixture now contains 1 mg in 10 ml and the required dosage can be obtained by giving 60 ml per hour which is equivalent to a drip rate of 60 paediatric micro-drops per minute or 20 standard drops per minute. This drip rate provides enough solution for an infusion time of 8 hours and 20 minutes. Contra-indications and Warnings, etc.** *Contra-indications* Isoket should not be used in the treatment of cardiogenic shock unless some means of maintaining an adequate diastolic aortic pressure are undertaken. Isoket is contra-indicated in circulatory collapse and severe hypotension. *Precautions* Close attention to pulse and blood pressure is necessary during the administration of Isoket infusions. *Adverse Effects* Whilst sharp falls in systemic arterial pressure can give rise to symptoms of cerebral flow deficiency and decreased coronary perfusion, clinical experience with Isoket has shown that this is not normally a problem. This is consistent with the known vasodilatory effects of Isosorbide dinitrate which occur predominantly on the venous rather than the arterial side of the circulation. In common with other nitrates, headache and nausea may occur during administration. **Pharmaceutical Precautions** *Compatibility* **Isoket contains Isosorbide dinitrate in isotonic saline and is compatible with commonly employed infusion solutions. No incompatibilities have so far been demonstrated. Isoket is compatible with glass infusion bottles and infusion packs made of polyethylene, e.g. Polyfusor (Boots) or Bottle-Paks and Flat-Paks distributed by Dylade, Cheshire. Isoket may be infused slowly using a syringe pump with a glass or rigid plastic syringe (Gillette Sabre syringe or Brunswick Disposable Plastipak syringes).** Isoket is incompatible with infusion bags and administration sets made from PVC and a loss of activity of up to 40% is possible on prolonged contact, e.g. 8 hours. Loss after 1 hour is approximately 30%. The use of PVC containers should therefore be avoided, e.g. Viaflex (Travenol) or Steriflex (Boots). **Legal Category** POM. **Package Quantities** Each pack contains ten ampoules of Isoket. **Further Information** Nil. **Product Licence** PL 4438/0001. **Basic NHS Cost** £49.50 per pack of 10 ampoules.

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*Trade Mark

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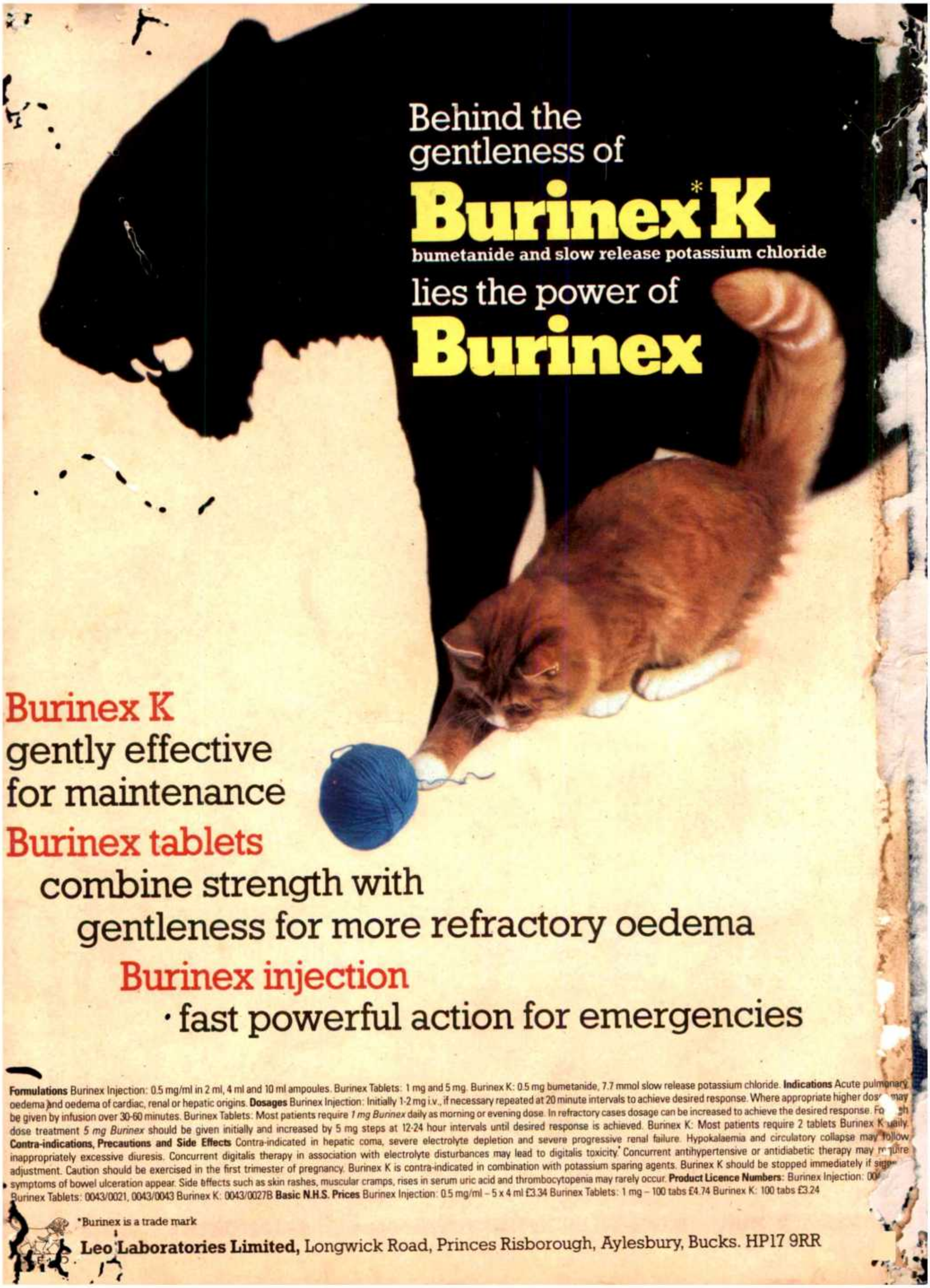

Behind the gentleness of

Burinex* K

bumetanide and slow release potassium chloride

lies the power of

Burinex

Burinex K
gently effective
for maintenance

Burinex tablets
combine strength with
gentleness for more refractory oedema

Burinex injection
· fast powerful action for emergencies

Formulations Burinex Injection: 0.5 mg/ml in 2 ml, 4 ml and 10 ml ampoules. Burinex Tablets: 1 mg and 5 mg. Burinex K: 0.5 mg bumetanide, 7.7 mmol slow release potassium chloride. **Indications** Acute pulmonary oedema and oedema of cardiac, renal or hepatic origins. **Dosages** Burinex Injection: Initially 1-2 mg i.v., if necessary repeated at 20 minute intervals to achieve desired response. Where appropriate higher doses may be given by infusion over 30-60 minutes. Burinex Tablets: Most patients require *1 mg Burinex* daily as morning or evening dose. In refractory cases dosage can be increased to achieve the desired response. For high dose treatment *5 mg Burinex* should be given initially and increased by 5 mg steps at 12-24 hour intervals until desired response is achieved. Burinex K: Most patients require 2 tablets Burinex K daily. **Contra-indications, Precautions and Side Effects** Contra-indicated in hepatic coma, severe electrolyte depletion and severe progressive renal failure. Hypokalaemia and circulatory collapse may follow inappropriately excessive diuresis. Concurrent digitalis therapy in association with electrolyte disturbances may lead to digitalis toxicity. Concurrent antihypertensive or antidiabetic therapy may require adjustment. Caution should be exercised in the first trimester of pregnancy. Burinex K is contra-indicated in combination with potassium sparing agents. Burinex K should be stopped immediately if sig[illegible] symptoms of bowel ulceration appear. Side effects such as skin rashes, muscular cramps, rises in serum uric acid and thrombocytopenia may rarely occur. **Product Licence Numbers**: Burinex Injection: 00[illegible] Burinex Tablets: 0043/0021, 0043/0043 Burinex K: 0043/0027B **Basic N.H.S. Prices** Burinex Injection: 0.5 mg/ml – 5 x 4 ml £3.34 Burinex Tablets: 1 mg – 100 tabs £4.74 Burinex K: 100 tabs £3.24

*Burinex is a trade mark

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